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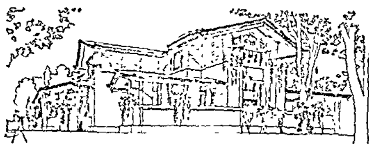
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AMEBIASIS

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Preface

DURING the 20 years since the Chicago hotel epidemic of amebic dysentery considerable new information has been amassed on the subject of amebiasis Fundamental studies have been carried out in the laboratory in an attempt to understand the physiologic pathology of *Endamoeba histolytica* Many practical investigations have likewise been conducted Diagnostic procedures have become more reliable, new drugs have been found to be highly efficacious in eradicating human amebiasis in the individual patient, and as a result the prognosis in amebic colitis and hepatic amebiasis has remarkably improved The practicing physician has gradually become impressed with the fact that amebiasis is frequently the underlying cause of a wide variety of illnesses and is not limited in its manifestations to acute dysentery and abscess of the liver Moreover, amebiasis is today recognized to be world-wide in its distribution and is not exclusively or primarily acquired in warm climates Credit for much of this progress is due to the courageous, persuasive endeavors of the late Colonel Charles F Craig and particularly to his two comprehensive volumes on amebiasis (1934 and 1944) Yet little or no progress has been made in community control of this disease.

It is timely that the problem of amebiasis should be reëvalu-

ated, to determine the extent of present-day factual information, and how this knowledge can be employed to safeguard the health of the individual and the community in which he lives. Improved methods of diagnosis and treatment can be utilized not only in curing individual patients suffering from the disease, but these same technics can be incorporated in comprehensive health programs looking forward to control of ameb infection in certain groups of the population.

Public consciousness of the importance of amebiasis as a dr bling disease in the community must be intelligently awaken This aspect of amebiasis has never been seriously develop There are ways of attacking the problem which are feasible practical, these can and must be put into effect as a part general program of personal hygiene and environmental sa tion.

This short monograph is intended to provide a concise, prehensive picture of amebiasis as a present-day clinica public health problem. In no sense is it an exhaustive trea the subject. Although it has been impossible to refer to a tributions even of major importance, it has seemed advi include in the bibliography all sources referred to in the few illustrations have been introduced to assist the r interpreting some of the more technical material w been presented

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Amebiasis

Chapter 1

Definition, Etiology, History and Geographic Distribution of Amebiasis

AMEBIASIS is an infectious, commonly chronic, non-inflammatory, frequently afebrile disease primarily involving the wall of the large intestine but at times extending to other soft tissues of the body. In contrast to shigellosis it is usually insidious in its onset, but on occasion acute symptoms may develop soon after exposure The incubation period is variable, from a few days to several months or more, depending on the amount of single or repeated exposure, on the virulence of the particular strain of the etiologic agent, on the presence or absence of pathogenic bacteria in the patient's intestinal tract, and probably on the state of his general well-being at the time of exposure

The manifestations of amebiasis are appropriately described as "protean" They vary as a result of the amount of tissue involvement and the anatomical location of the lesions. Thus, in intestinal amebiasis they may consist of fulminating dysentery or may mimic acute appendicitis, peptic ulcer or gallbladder disease Again, there may be long periods of remission between acute symptoms. In the average case the manifestations are less severe, and in many infected individuals the disease is asyndromic or even apparently asymptomatic. Amebiasis of organs and tissues outside the large intestine is invariably

secondary to intestinal infection. Certain of these varieties of the disease are accompanied by a moderate degree of leukocytosis and fever. Bacterial invasion of the primary amebic lesion modifies its architecture and invariably complicates the clinical picture.

ETIOLOGY

The etiologic agent of amebiasis is a microscopic one-celled animal, *Endamoeba histolytica*. It belongs to the Phylum Protozoa, Class Rhizopoda, Family Amoebidae. The more common synonyms of this ameba are as follows: "Amoeba coli" Lösch, 1875; "Amoeba dysenteriae" Councilman and Lafleur, 1891; *Entamoeba histolytica* Schaudinn, 1903; *Entamoeba dysenteriae* Craig, 1905; *Entamoeba tetragona* Hartmann, 1908; *Entamoeba hartmanni* von Prowazek, 1912; *Endamoeba dysenteriae* Kofoid, 1920, and *Entamoeba dispar* Brumpt, 1925. There is a dispute as to whether the generic name should be "*Endamoeba*" or "*Entamoeba*." Since *Endamoeba* is the more commonly employed designation in American medical literature this name will be used in this monograph

Endamoeba histolytica has five successive stages in its life cycle, viz, trophozoite, precyst, cyst, metacyst and metacystic trophozoite. All of these stages occur in the human intestine. The *trophozoite* is the active, growing, multiplying stage, the one which invades tissues and produces lesions. It moves by means of pseudopodial extensions of its ectoplasm, progressing into undamaged tissues by lytic digestion. The digested material is then taken into the ameba and serves the metabolic needs of the organism. Multiplication and colonization result from binary fission, whereby two daughter amebas are produced from the parent. Under favorable conditions this numerical increase takes place every few hours and may con-

tinue indefinitely. As long as *E. histolytica* remains in the tissues it is in the trophozoite condition. This is also the exclusive or predominant stage in a diarrheic or dysenteric stool. Although in cultures and in the intestinal canal *E. histolytica* ingests bacteria like the non-pathogenic amebas of the intestinal canal, there is no substantial proof that this occurs when *E. histolytica* becomes a tissue parasite.

During the dehydration of the feces in the lower levels of the colon *E. histolytica* free in the feces discards all undigested inclusions and rounds up. This is the *precystic stage*. Shortly thereafter it secretes a thin, tough membrane (the cyst wall) around itself and becomes encysted. At first the cyst is uninucleate but as it matures it becomes binucleate, then quadrinucleate. This ripening of the cyst may take place in the rectum after the stool has been formed or after the stool has been passed, but trophozoites evacuated in a frankly diarrheic or dysenteric stool do not encyst, even though the stool may later become partly formed as a result of drying.

The *cyst* is the transfer stage of the infection from one person to another. When it is taken into the mouth in a viable condition and is swallowed, it passes in an unaltered condition through the stomach and proximal portion of the small intestine. On arrival at a level where the pH is neutral or slightly alkaline, the encysted organism becomes activated, ruptures its cyst envelope and escapes as a naked protoplast, the *metacyst*. Synchronously or soon thereafter cytoplasmic division corresponding to the number of nuclei of the metacyst results in the production of minute *metacystic trophozoites*. These pass through the remainder of the small intestine into the cecum, where, on sufficient contact with the cecal mucosa they are able to digest minute cavities in the outer portion of the mucosal cells, thus completing the cycle and initiating tissue infection. The morphologic characters and life cycle of *Endamoeba histolytica* are diagrammatically represented in Figure 1.

HISTORY

Although early workers in India undoubtedly saw many cases of acute amebic colitis, and both Lewis (1870) and Cunningham (1871) found amebas in stools of cholera patients, these investigators failed to recognize that the associated amebas were the cause of the dysentery.

Discovery of amebiasis as a distinct type of disease is usually attributed to F. Losch, a clinical assistant in medicine in St. Petersburg, Russia (1875) Upon examining the stools of a patient with relapsing dysentery, Losch found active amebas with ingested red blood cells. He inoculated some of the dysenteric stool into dogs, both by mouth and by rectum, and was able to produce dysentery in these animals He regarded the amebas as contributory rather than the primary agent of the disease and named them "Amoeba coli." At necropsy of the patient there were numerous lesions of the large intestine, together with many amebas in the ulcers and free in the intestinal contents Thus, all evidence indicates that Losch observed both the amebic lesion and its causal agent, *Endamoeba histolytica*, although he failed to appreciate their significance

Following Lösch's publication, Koch (1881) and Kartulis (1886), working in Egypt, demonstrated the pathogenic relationship of these amebas to "tropical dysentery," while Kartulis found them in the necrotic tissues of the liver (1887) and in a brain abscess (1904) Meanwhile Hlava (1887) in Prague,

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wall as naked protoplasts, the *metacysts* (B_7) Each metacyst divides to form as many little *metacystic trophozoites* (B_8) as there are nuclei in the metacyst These little amebas are carried in the fecal stream into the cecum If they lodge in the mucosal gland crypts they feed on mucus secretions, grow into normal-sized trophozoites (B_9), produce superficial erosion of the mucosal cells and start colonizing, *LL* represents the intestinal lumen, *TT*, the tissues of the intestinal wall invaded and colonized by this ameba

Osler (1890) in Baltimore, Stengel (1890), Musser (1890) and Dock (1891) in Philadelphia, and Quincke and Roos (1893) in Kiel made valuable clinical contributions to the disease. In 1891 Councilman and Lafleur published a classical study on the pathology of amebic colitis and liver abscess, a contribution which is as timely today as it was when it appeared. Richard P Strong (1901), in Manila, differentiated the pathogenic ameba (*Endamoeba histolytica*) from the common colon type (*Endamoeba coli*) and reported that dysentery of amebic origin was more prevalent in the Philippines than bacillary dysentery. Later Walker and Sellards (1913), likewise working in the Philippines, conclusively demonstrated in human volunteers that *Endamoeba histolytica* produces disease while *Endamoeba coli* is innocuous.

Gradually the concept "amebiasis" became enlarged as a result of epidemiologic and clinical investigation. More exact criteria were likewise developed for the diagnosis of *Endamoeba histolytica* and its differentiation from *E. coli* and other species of non-pathogenic intestinal amebas (*Endolimax nana, Iodamoeba bütschlii* and *Dientamoeba fragilis*). Surveys for amebiasis in several countries now provided evidence that the disease was not confined to tropical areas but was essentially cosmopolitan in its distribution. Moreover, increased knowledge indicated that the original designations "amebic dysentery" and "amebic liver abscess" constitute only small segments of the entire clinical picture of the disease. Amebic colitis might be acute, subacute, chronic with acute relapses, asyndromic or asymptomatic; hepatic amebiasis might consist of acute hepatitis or the more chronic sequela, amebic liver abscess Thus, physicians and parasitologists have come to appreciate that amebiasis is a relatively common infection of manifold symptoms and must be considered as a possible primary or contributory cause of ill-health anywhere in the world.

GEOGRAPHIC DISTRIBUTION

The early conception of amebiasis as a disease confined to the tropics was a natural one, since dysentery and liver abscess, which were commonly encountered in warm climates, are dramatic in character and can be readily distinguished by the clinician and substantiated by the pathologist. Although these types of the disease possibly occur less frequently now than they formerly did in the tropics and are not often observed in cooler areas of the world, there is no reason to believe that infection with *Endamoeba histolytica* has become less cosmopolitan than it was 50 years ago.

Impetus for study of the geographic prevalence and incidence of amebiasis in different populations throughout the world may be traced in part to the study of Wenyon and O'Connor (1917) on the intestinal protozoa of man in the Near East and that by Dobell and associates (1918) of 1300 convalescent British soldiers who had been stationed in France, the Near East, Middle East and India during World War I. This lead to surveys of *E. histolytica* infection among natives of Great Britain who had never left the country but were found to be infected with *Endamoeba histolytica*. As early as 1913 Giffin reported 4.6 per cent incidence of amebiasis in 1700 patients at the Mayo Clinic, while Sanford (1916), in a study of 5000 patients from this Clinic found 10.7 per cent infection. Most of these cases originated in Midwestern United States and adjacent Canada. In a summary of routine clinical laboratory examinations of 8029 persons in federal and state hospitals and training schools in the United States, Boeck and Stiles (1923) found 4.1 per cent infection. By 1926 Craig had sufficient evidence to estimate that approximately 10 per cent of the population of the United States are infected with *E. histolytica*. Figures up to 1951 on 118,156 *E. histolytica*-positive indi-

viduals in this country, for the most part examined only o provide an average incidence of 8.1 per cent (Craig and F 1951). It is not improbable, then, that multiple examina would have doubled this figure. These data were obtained surveys on different groups of the population, viz., urba rural, "healthy" and patient groups, of various professio occupations, in homes and institutions, from early inf old age, and covering all important geographic region United States. The incidence percentage in this cros varied from 1 4 in New England college students to rural Tennessee and 40.0 to 55 0 in eleemosynary in (Craig and Faust, 1951, p. 72).

In the Western Hemisphere exclusive of the Uni amebiasis has been found to be indigenous to E Western Canada (Porter, 1934; Miller, 1939; Choquette, 1947) and Alaska (Hitchcock, 1950). endemic in all states of Mexico in which survey conducted (Beltrán and Mazzotti, 1951); in Cen (*Rev Med. Honduras*, 1941); the West Indies Haiti (Williams and Thomas, 1930), the Domi lic (Mackie *et al.*, 1951) and northern South A and Faust, 1951). Extensive surveys in Argentin it is indigenous in populations as far south a Magellan (Castex and Greenway, 1934).

In Europe amebiasis prevails from Scandin 1928) to the Mediterranean coast (Cart Matthews and Smith, 1917); in Africa it along the north and northeastern coasts (R Wenyon, 1916) and in Natal (Elsdon-Dew formation concerning its prevalence througho is too meager for evaluation. North China (son, 1924, Tao, 1931), Manchuria (Hiyeo China (Faust and Wassell, 1921), U.S.S Zerchaninov, 1933), Korea (Kessel, 192

and Davis, 1948), the Philippines (Tobie, 1945), Malaya (Jepps, 1923), Java (Brug, 1920) and the islands of the Southwest Pacific (Markell, 1945), all provide evidence that human infection with *Endamoeba histolytica* is common and widely disseminated. It is reasonable to believe that other areas of the globe, as yet unsurveyed, are likewise endemic or hyperendemic for amebiasis.

Thus, amebiasis probably exists in all native populations throughout the world from the Arctic to the Antarctic Circles

ummary

1. Amebiasis is an infection produced by *Endamoeba histolytica*, the only ameba of man which has been demonstrated to invade tissue.
2. *E histolytica* has five successive stages in its life cycle, viz., trophozoite, precyst, cyst, metacyst and metacystic trophozoite. All of these stages are found in the human intestine Propagation occurs by binary division of the trophozoite, which is the tissue stage. Trophozoites are evacuated in dysenteric and diarrheic stools, cysts in formed stools.
3. *E. histolytica* was first seen by Lösch (1875), in St. Petersburg, Russia, who recovered it in a dysenteric patient, successfully inoculated dogs with the organism, and later recovered it in intestinal ulcers when the case came to autopsy
4. Strong (1901) first proposed that *E. histolytica* is associated with tissue destruction and that *Endamoeba coli* is a harmless parasite. Walker and Sellards (1913), using human volunteers, confirmed this hypothesis.
5. For many years amebiasis was regarded as essentially a tropical disease. Only acute amebic dysentery and amebic abscess were recognized as clinical entities. With the de velopment of dependable laboratory diagnosis, surveys an clinical studies were made in representative countries the World It has been found that amebiasis is cosm politan in its distribution and extremely varied in its ma festations.

Chapter 2

The Natural History of Amebiasis

In Chapter 1 information has been presented concerning the stages which typically succeed one another in a complete life cycle of *Endamoeba histolytica*, the etiologic agent of amebiasis. The tissue phase of the organism is the trophozoite or active stage, and under favorable conditions this stage may continue to multiply more or less indefinitely wherever an equilibrium is established between pathogen and host tissue, so that tissue repair keeps pace with tissue destruction. If destruction exceeds replacement the damage may become irreversible, producing a situation unfavorable alike to host and parasite (i.e., death). If tissue replacement in the infection outdistances colonization of the ameba, spontaneous clearance may occur, with complete recovery of the host and extinction of the parasite. Overwhelming tissue destruction by *Endamoeba histolytica* has been demonstrated repeatedly in man and in experimental infections of susceptible laboratory animals. Spontaneous cure of the infection has been observed many times in laboratory animals and indirect evidence indicates that it occurs in human cases (Faust, 1941).

Encystation does not take place in the tissues but only after the progeny of the tissue invaders have been extruded from the

Summary

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Encystation does not take place in the tissues but only after the progeny of the tissue invaders have been extruded from the

lesions and are in process of discharge from the intestinal tract. If irritation of the colonic and rectal mucosa is considerable, dehydration of the feces does not occur and the amebas are discharged as trophozoites; but if the lower portion of the colon and the rectum remain essentially undamaged and dehydration proceeds normally, the amebas round up and become encysted The actual cause of encystation under these circumstances is not known but it is probably not dehydration per se, since *E. histolytica* encysts in a liquid culture medium, particularly when overpopulation develops (Everritt, 1950).

In so far as man is concerned, the viable cyst is the stage for transmission. Experimental study on dogs, using human strains of *E. histolytica* (Swartzwelder, 1939), indicates that unripe (uninucleate and binucleate) as well as ripe (4-nucleate) cysts, when fed or when introduced by tube intragastrically, excyst and produce tissue invasion. Thus, maturing of the cyst before its exit from the bowel or in the extrinsic environment is not essential to a new infection. However, in so far as is known, once a cyst has been formed in the colon or rectum, excystation does not occur before it is evacuated in the stool (Swartzwelder, 1939); for normal excystation the cysts must be introduced by way of the mouth.

STAGE OF EXTRINSIC EXISTENCE AND SURVIVAL OF *ENDAMOEBA HISTOLYTICA*

Outside the host's body the cyst of *E. histolytica* is subject to a variety of unfavorable conditions, since the thin cyst wall will not protect the enclosed organism for any length of time against desiccation or putrefaction in the environment. If cysts of *E. histolytica* get under fingernails they soon succumb to drying (Spector and Buky, 1934; Andrews, 1934). Cysts of *Endamoeba coli* appear to be much more resistant (Reardon, Verder and Rees, 1951). Likewise, cysts of *E. histolytica* do

not survive long in undiluted feces in which putrefactive and fermentative bacteria are active. On the other hand, if the feces are diluted by large quantities of water so that putrefactive action is minimal, the cysts may remain viable for several months (Boeck, 1921) Moreover, cysts in formed stools at icebox temperature (5–8°C) remain alive for one to two weeks, even though the cytoplasm of the organism becomes granular Thus, the survival of the cyst of *E. histolytica* outside the body of the host varies in time from a few minutes to as long as three months or possibly longer, depending primarily on unfavorable or favorable environmental conditions this constitutes an important aspect of the epidemiology of amebiasis.

ANIMAL RESERVOIRS

Man is not the sole host of *Endamoeba histolytica,* since several animals are infected in nature In so far as studies have been made, practically all species of monkeys harbor an ameba which is morphologically, biologically and pathogenically indistinguishable from *E histolytica* of man Moreover, dogs are naturally parasitized by this same organism (Faust, 1931b; Andrews, 1932, Kubo, 1936) In North China Kessel (1928) found pigs harboring this ameba, but this observation has not been confirmed for other localities Investigators have also reported infection in the rat (Andrews and White, 1936). The kitten, guinea pig, hamster and rabbit are good laboratory hosts of *E histolytica,* but natural infection in these hosts has apparently not been demonstrated

SOURCES OF HUMAN EXPOSURE

Human infection with *Endamoeba histolytica* results only when viable cysts get into the mouth and are swallowed The sources for this contamination are multiple: any one or more of

these may be responsible for human exposure. The more important sources consist of water, food, and contaminated fomites. Each of these will be considered briefly.

Water. In tropical areas where drinking water is grossly polluted with sewage a vicious cycle has frequently been responsible for high prevalence of amebiasis, with numerous cases of acute amebic dysentery and liver abscess. This situation existed in Manila, Calcutta and Cairo 50 years ago, and in the Panama Canal Zone before installation of sanitary water and sewage-disposal systems. And it exists today in many tropical and subtropical urban centers where group hygiene is endangered as a result of inferior sanitary engineering. Moreover, water supplies from safe sources in the temperate zone may become contaminated by backflow of sewage from faulty plumbing. A striking example is that of the epidemic of amebiasis which developed in a Chicago hotel during the late summer of 1933, when there were over 1400 cases of amebic dysentery, with more than 100 deaths, among the guests and employees of a hotel (Bundesen, 1934). The following spring a water-borne epidemic of this disease broke out in a group of individuals fighting a fire in the Chicago slaughterhouses, attributed to drinking water from the Chicago drainage canal which was intended only for watering the livestock (Hardy, 1935). More recently (1946–1947) there was an epidemic of amebiasis of water-borne origin in an apartment building in Tokyo, in which 161 American Occupational Force personnel and 248 Japanese employees were exposed (Ritchie and Davis, 1948). About 80 per cent of the Americans had intestinal symptoms associated with the presence of *E. histolytica* in their stools (Davis and Ritchie, 1948). Still another recent epidemic of acute amebic colitis has been reported among personnel from a permanent Royal Air Force station in England, most of whom had never been outside the country. The cases developed during the latter half of 1950 and had their origin in

"drinking water grossly polluted with sewage" from the base (Morton, Stamm and Seidelin, 1952)

One may conclude with Craig (1944) "These epidemics of amebiasis prove that, given a grossly polluted water, thus insuring massive doses of cysts, and the partaking of this water by large *numbers of individuals*, amebiasis and amebic dysentery may become epidemic just as other intestinal infections"

In contrast to epidemic outbreaks of amebiasis resulting from heavy contamination of drinking water with cysts of *E histolytica*, potential exposure may occur from use of water sparsely seeded with these cysts. This situation presumably exists in urban water supplies, at times when filtration or sedimentation is faulty, and in hundreds of thousands of rural communities where household water is not inspected for seepage contamination. Theoretically a considerable amount of amebiasis throughout the world may be credited to this source, although no direct proof has ever been provided

Food Food constitutes a considerable source of exposure to amebiasis. Contamination of the food with cysts of *E histolytica* may result from (1) vegetables used as salad greens and strawberries grown on soil fertilized with human manure; (2) comestibles to be eaten raw which are washed in grossly polluted water, (3) green salads, raw fruits and cold meats, contaminated by cooks and other foodhandlers who are cyst passers and do not observe clean habits following defecation; and (4) food to be served cold which has been contaminated by filth flies and other insects.

Circumstantial evidence provides numerous examples of persons in tropical and Oriental countries who consume raw lettuce and strawberries and sooner or later develop acute amebic colitis Yet there is no actual proof that these dietary habits per se are responsible for the disease Mills, Bartlett and Kessel (1925) and Johns (1930) were unable to recover cysts of *E. histolytica* from green foods known to be contaminated, and

were obliged to conclude that this method of transmission was not necessarily an established fact.

The question of foodhandlers who are cyst passers deserves serious consideration Cooks, helpers who prepare salads and cold meats, and waiters who serve food and harbor *E. histolytica* are all potential transmitters of amebiasis. More frequently than not these persons who have contact with food in restaurants and in the home fail to wash their hands thoroughly after defecation. Possibly the casual rinsing of the fingers in water without scrubbing them is a more serious breach of personal hygiene than allowing the cysts to dry in minute amounts of feces on the tips of the fingers or under the fingernails, since drying destroys while moistening will prolong the viability of the cysts, which are the more readily transferred to salad greens and cold meats.

There is substantial indirect evidence that foodhandlers are important in the transmission of amebiasis The committee of experts appointed to study the Chicago hotel epidemic concluded that the high frequency of cyst passers in the restaurant service of the hotel was probably an important contributory factor to the epidemic, even though gross sewage contamination of drinking water was considered to be the principal cause (McCoy *et al.*, 1936). A convincing case is that reported by Schoenleber (1941) for an industrial community on the island of Aruba, off the coast of Venezuela. All water and food came from ameba-free sources in the United States, and there was a modern sewage-disposal plant. Nevertheless 25 per cent of the persons on the island were infected with *E. histolytica*, 14.4 per cent of whom had clinical amebic colitis. The infection rate of the Chinese foodhandlers was 33 per cent. Antiamebic treatment of this group was carried out until they were free of the parasite; in a single year the incidence rate in the untreated inhabitants fell 50 per cent and in three years, 90 per cent. The comparable percentage decrease in amebic colitis was 86 in one

year and 92 in three years. Meleney (1930) and numerous other workers have emphasized the positive correlation of familial amebiasis and infection with *E. histolytica* in the mother or servant in the household who prepares the food. Foodhandlers who harbor *E. histolytica* should be regarded as a definite hazard in the transmission of the infection.

Filth flies and other household insects. These undoubtedly contribute substantially to the over-all picture of the mechanical transmission of amebiasis Experimentally, and by dissection of the housefly (*Musca domestica*) and other feces-eating flies, it has been demonstrated repeatedly that these insects avidly feed on feces, and that in endemic areas of amebiasis living cysts of *Endamoeba histolytica* are not damaged by the intestinal juices of the fly and are discharged several to many hours later in a viable state, either in vomit drops or fecal dejecta (Thomson and Thomson, 1916, Wenyon and O'Connor, 1917, Roubaud, 1918, Buxton, 1920, Root, 1921; Frye and Meleney, 1932, Harris and Downs, 1946; Pipkin, 1949). However, cysts of *E histolytica* are rapidly destroyed in feces which become attached to the external mouth parts, wings, legs and body bristles of these flies (Pipkin, *l c.*). The American cockroach (*Periplaneta americana*) has likewise been incriminated as a mechanical vector of cysts of this ameba (Macfie, 1922, Tejera, 1926; Frye and Meleney, 1936).

As in other enteric infections, so in amebiasis, filth flies constitute a serious public health menace in localities where they are allowed to breed They were reportedly responsible for an outbreak of amebic colitis among U. S Army troops at El Paso, Texas in 1916 (Craig, 1917). Similarly, in 1921, the author observed an epidemic of the disease among a group of foreign physicians to whom he was giving a course in tropical medicine at a hill station in Central China There was no amebic infection in the colony and a sustained program to control the breeding of houseflies was producing satisfactory results However, a

high incidence of amebiasis was discovered in a Chinese village several miles distant across the valley. A few days later a strong wind brought swarms of flies from the village into the summer colony. Within two weeks there were several active cases of amebic dysentery in the hill station, including some among the postgraduate physicians.

Fomites. Another source for transmission of amebiasis, which is much more important than is usually suspected, is direct person-to-person transmission or through the intermediary of clothing and other fomites. This method is probably very common in areas of hyperendemicity, such as in tropical countries, in rural communities in the southern part of the Appalachian highlands in the United States and in eleemosynary institutions throughout the world. The author has personally observed this correlation of hyperendemicity and low state of individual and group hygiene in native villages in Panamá, in Mexico, on the island of Leyte in the Philippines, and in North and Central China, in all of which areas the incidence of amebiasis is high, and where water, food and filth flies fail to provide a satisfactory explanation for the relatively high endemicity of the infection in the area. Undoubtedly many other native communities have a sustained high rate of infection with *E. histolytica* as a result of direct contamination.

Amebiasis in prisons, mental hospitals and children's asylums has been so commonly reported that it seems unnecessary to furnish supporting evidence. In the average prison and public mental institutions sanitary conditions are frequently deplorable, hence it is no surprise that amebiasis, once introduced, has an opportunity to become widely disseminated among the inmates. In contrast, children's asylums usually appear clean and well maintained. It is therefore something of a shock to discover that here, too, the incidence of the infection greatly exceeds that of the non-institutionalized population of the same community.

A careful epidemiologic study of a children's home in New Orleans was reported by Ivanhoe in 1943. This is an institution which cares for foundlings from birth to seven years of age, under the direct care of devoted religious sisters. The water and sanitary facilities were of high grade, as certified after a detailed inspection by the State Sanitary Engineer. The kitchen was clean and the food was properly prepared. There were almost no flies on the premises during more than a year of investigation. Fecal examinations revealed no amebiasis in the youngest group who were cared for by the sisters, 43.3 per cent incidence among those of the intermediate group who were learning to care for themselves, and 56.4 per cent among the oldest group who were nearly self-sufficient in so far as bathing, use of the toilet and dressing were concerned. Cysts of *Endamoeba histolytica* were isolated from the hands and soiled underwear of the children of the infected groups, the bottom of their laundry chute, damp sand in the play box, and sediment on the concrete bottom of the bathing pool. Ivanhoe (*l.c.*) suggested that transmission occurred as a result of "direct contact transfer aided by the general pollution of the environment."

Not only is amebiasis apt to be prevalent in institutionalized groups in warm climates, but its incidence in cooler climates is higher than that of the general population (Matthews and Smith, 1919, Svensson, 1928, Miller, 1939).

A potential but unproven source of viable amebic cysts in warm areas is moist ground which is heavily polluted by the promiscuous defecation of infected small children (Beaver and Deschamps, 1949a). These and other children playing on the contaminated damp soil, especially in recovering candy and play objects dropped on the ground, conceivably may acquire amebic infections just as they contract ascariasis.

Animal reservoirs of *Endamoeba histolytica*. These constitute still another potential source of infection for man. Monkeys of many species throughout warm climates of the

Eastern and Western Hemispheres are infected with
which has been shown to be identical with that whi
the intestinal wall of man (Dobell, 1931; Johnson,
tropical villages near forests where these animals liv
considerable contact between man and monkeys Thi
opportunity for repeated human exposure to infection
viding polluted surroundings, just as in man-to-man tr
sion. Moreover when these monkeys are imported into
climates as pets or for laboratory purposes, they usually
their infection for a considerable period of time, and thu
stitute a source of exposure for persons many hundreds of
distant from the jungles where the monkeys breed.

From time to time in subtropical and tropical areas of
globe dogs are found to harbor *Endamoeba histolytica*,
occasionally small epizoötics of amebic dysentery have be
reported (Boyd, 1931). However, the incidence of this ame
in the dog is low compared with that in man, so that it is muc
more reasonable to believe that the dog gets its infection fron
man rather than that the dog serves as an important source o
the infection for man This conclusion is supported by the
additional evidence that the usual stage of the ameba discharged by the dog is the trophozoite rather than the cyst.

While rats which infest human habitations may contaminate food with their fecal dejecta, these pellets dry out rather rapidly so that the cysts of *E. histolytica* which may be discharged by infected rats will soon die. Thus, the rat is not to be regarded as a particularly likely source for human exposure to infection with *Endamoeba histolytica*. Other domestic animals, including pigs, appear to provide little opportunity for exposure.

From available information it is concluded that monkeys are the only animals which probably constitute any considerable potential source of amebiasis for man. Epidemiologically expressed, the almost invariable reservoir of amebiasis for

human infection is man himself, who constitutes a continuing chain of the infection.

EXPOSURE VS. INFECTION

Exposure to amebiasis has been shown to result for the most part from introduction into the mouth of cysts of *Endamoeba histolytica* present in polluted water and food, or as contaminations on fomites which have been soiled by excreta of infected persons. The inoculum at times consists of a single heavy dose of cysts sufficient to provide a large number of active amebas, under which circumstance the chance of infection is remarkably good. This is probably the usual underlying cause of epidemics of amebiasis in individuals previously not subjected to exposure. Under such favorable conditions for the amebas this epidemiologic situation occurs occasionally in temperate climates viz., Chicago hotel (McCoy *et al*, 1936a); Chicago stockyard fire (Hardy, 1935); Tokyo apartment building (Ritchie and Davis, 1948). More often it results in fulminating amebic colitis in tourists or commercial travelers who have visited hyperendemic foci of amebiasis in tropical areas, and in military personnel who are exposed while on duty in such areas.

In a majority of exposures to amebiasis the inoculating dose is light. Possibly only a few cysts are ingested at any one time and the chance is minimal that one or more of these exposures will produce infection. But given repeated light exposure, sooner or later infection may take place and tissue invasion develop. This method is the one which is probably responsible for the wide prevalence of amebiasis in temperate zones, as in the United States and Europe. Many of these infections are asymptomatic or asyndromic but some are more serious in their manifestations.

A third epidemiologic type is that of constant exposure to

heavy doses of cysts of *E. histolytica*. Examples of this type are found in many native communities in warm climates, likewise in the southern Appalachian highlands in the United States and in eleemosynary institutions throughout the world. While acute clinical infections occur in these groups, most of the individuals apparently have been repeatedly exposed, many from early childhood, to the same strain of the ameba, and have developed considerable tolerance to it. Typically these persons pass millions of cysts in their stools daily and thus saturate the environment with the inoculum.

VIABILITY, INFECTIBILITY AND VIRULENCE OF STRAINS OF *E. HISTOLYTICA*

Viability and infectibility. Even though cysts of *Endamoeba histolytica* are capable of retaining their vitality for weeks or months under favorable conditions outside the human body, and even though they may be demonstrated to produce tissue invasion in suitable experimental animals, they exhibit a wide range of infectibility (Faust *et al.*, 1946). This variability in infectiveness for the experimental test animal may have a parallel in human amebiasis, although it would not be safe to conclude that human and animal susceptibility to infection are necessarily identical.

Virulence of strains. Like bacteria, viruses, rickettsias and spirochetes, different strains of *Endamoeba histolytica* have intrinsic differences in virulence. Some parasitologists have concluded that the size of the cyst is a criterion of virulence: they regard small races as relatively non-pathogenic and large races as pathogenic (Sapero *et al.*, 1942). However, Meleney and Zuckerman (1948) and the author (unpublished studies) have demonstrated that under favorable conditions "small races" of *E. histolytica* transform into "large races," thus suggesting that racial size is inconstant and therefore does not constitute a dis-

tinct index of virulence Moreover, Kessel (1928a) and Frye and Meleney (1938) have demonstrated that cysts of small size from human cases produce lesions in experimental kittens, and the author and his colleagues have recently discovered a case of symptomatic amebiasis in a child passing cysts of *E. histolytica* averaging 7 microns in size

A second difference in virulence (e g, pathogenicity) has come to be associated with strains of *E histolytica* recovered from acute infections on the one hand and from carrier states on the other In Continental Europe most physicians and medical parasitologists believe that amebiasis of local origin is not clinically important, even though there is a considerable frequency of infection (Reichenow, 1931; Westphal, 1938). Brumpt (1925) even went so far as to provide a different name (*"Entamoeba dispar"*) for strains of *E histolytica* which were morphologically identical but were regarded as non-pathogenic Likewise, in England, Hoare (1950) has suggested that the indigenous strains of this organism in the British Isles are essentially avirulent Moreover, clinical studies in certain population groups in the United States, e g, rural localities in Eastern Tennessee in contrast to urban infections in the vicinity of Memphis (Meleney and Frye, 1933), and in an institutionalized group of children in New Orleans (unpublished data of the author) would seem to indicate that these infected individuals suffer little or no inconvenience from the infections Yet, when these strains of *E. histolytica* were inoculated into susceptible laboratory animals (kittens, Meleney and Frye, *l.c.*, dogs, Tobie, 1940), tissue invasion and destruction occurred

In so far as different strains of *E histolytica* have been adequately tested in susceptible animals, no strain has been demonstrated to be lacking in virulence. Neverthless, different strains do exhibit different degrees of virulence, both in the human host and in test animals (dogs, kittens, guinea pigs, etc.) Finally, it has been shown by Faust and Swartzwelder (1935)

and Meleney and Frye (1937) that with continuous passage of *E. histolytica* from animal to animal the strains become increasingly pathogenic, i.e., their virulence becomes enhanced. This possibly suggests that in human amebiasis the rapid transfer of viable cysts from man to man, particularly in newcomers to an endemic area, may be responsible for certain epidemic outbreaks of the disease. This parallels the situation which has been demonstrated many times for malaria, epidemic typhus fever and yellow fever.

HUMAN SUSCEPTIBILITY TO INFECTION

Fundamentally there is no evidence supporting the thesis that there is any difference in susceptibility to infection with *Endamoeba histolytica* as a result of race, age or sex. The factors influencing susceptibility are relatively intangible but they probably include the amount and quality of basic diets, temperance or indiscretion with respect to food, drink and physical exercise, and climatic adaptation; possibly partial immunity if the individual is reexposed to the same strain which previously produced infection, and supervening disease of other etiology. Usually these factors are so intermingled that it is difficult, if not impossible, to separate them, so as to state which are the determining ones in any particular instance.

Race. Kessel and Svensson (1924), in a comparative study of the intestinal protozoa in Chinese and American-European groups in Peking, China, found practically the same incidence of infection with *E. histolytica* in the two racial groups. Moreover, Ritchie and Davis (1948) found infection of essentially the same frequency in American residents and Japanese employees in Tokyo, Japan. Nickel (1942) in a study of intestinal parasites in Mississippi, reported a higher incidence of *E. histolytica* in one county where there was a sizeable American Indian population, but the lower economic conditions and sani-

[illegible] standards of this group could well explain this finding The [illegible] of observations with reference to [illegible] ation in Durban, Natal, [illegible]) Here there are three racial groups, Europeans, Hindus and native Bantus The Europeans have a moderate amount of amebiasis, with only an occasional case of acute amebic colitis Infection is relatively intense and widespread in the Hindus but with infrequent clinical manifestations They probably constitute the "seed-bed" of the infection in the area In contrast, amebiasis is both prevalent and of fulminating character in the Bantus, and is not readily controlled by anti-amebic drugs Elsdon-Dew (*l c*) regards this difference in the racial tolerance or intolerance to the disease to be due to basically different diets

Physicians who have had experience in tropical areas know how rapidly some Americans or Europeans acquire acute amebic dysentery in these countries, viz, Panamá, the lowlands of Mexico and Central America, coastal Colombia, Venezuela, the Guianas, Northern Brazil, Morocco, Egypt, India, Indo-China and the Philippines. On the other hand, other persons from temperate zones who visit or come to reside in these same countries remain free of the disease Usually the incidence of amebiasis in the indigenous populations in these countries is high but infections of clinical grade are relatively few. These carriers provide the inoculum not only for repeated reinfection of their own groups but for foreigners who do not pay meticulous attention to their food and drink

Information on racial susceptibility to amebiasis is unfortunately not subject to statistical analysis but it indicates that, irrespective of race, wherever there is sufficient exposure, infection occurs

Age. Amebiasis is no respecter of age; it occurs from earl[illegible] infancy to old age Many surveys for intestinal infections ha[illegible]

been conducted on children of school age because of the relative ease of obtaining stool specimens for examination. Infection with *E. histolytica* has invariably been found in this age group. Moreover, amebiasis has been reported from time to time in infants (LeRoy des Barres, 1930; Howell and Knoll, 1941), although they are less frequently infected than older children because of less frequent exposure. In children's asylums the incidence in percentage of individuals infected is characteristically much higher than in the general population of the same age group, due to a building up of inoculum within the group (Ivanhoe, 1943).

In an analysis of 4,000 clinic patients in New Orleans the author (1933) found approximately 6 per cent infection with *E. histolytica* in children of pre-school age, 15 per cent in those six to 10 years of age, 20 per cent in the next quinquennium, and a peak incidence of over 40 per cent in the 26 to 30 age group. The incidence curves of Milam and Meleney (1931) for 374 persons in a rural area of Tennessee and of Meleney, Bishop and Leathers (1932) for 20,237 rural inhabitants throughout the same state follow the same trend as that of the author (*l.c.*) but at a higher level, with a maximum at the same period of life but with a more sustained high incidence until 60 years of age, when it more rapidly declines. The meaning of these incidence curves is not that there is a difference in susceptibility but probably a cumulative exposure up to about 30 years of age or more, then a decrease as the older years bring less contact paralleling decreased activity.

Sex. Wherever a large cross-section of a population has been surveyed, viz., North China (Tao, 1931) and New Orleans (Faust and Headlee, 1936), there has been essentially no difference in the percentage of infection of males and females, although a slightly higher frequency has been reported for males. On the other hand, the incidence figures for acute amebic colitis (Simon, 1912; Brown, 1922; Strong, 1925; Hinman and

Kampmeier, 1937) show a high preponderance of males over females, i e., from 4.1 . 1 to 5 · 1. Moreover, amebic liver abscess is much more commonly diagnosed in men than in women (Ochsner and De Bakey, 1943) There is no statistically significant evidence supporting the view that males are more susceptible than females, but no satisfactory explanation has been provided for the reported preponderance of acute amebic colitis and amebic liver abscess in males

Food habits and susceptibility If information on the incidence of amebiasis in population groups were carefully analyzed, there would probably be considerable evidence supporting the view that a high carbohydrate, low animal protein diet predisposes to high prevalence of infection (Alexander and Meleney, 1935) Natives of tropical climates, whose basic diet is starch and lacks essential proteins and vitamins, commonly suffer from malnutrition and have a concurrent high incidence of amebiasis Elsdon-Dew (*l c*) has attributed the widespread clinical manifestations of amebiasis in the Bantus of Natal to a maize diet

Experimentally Hegner (1924) found that intestinal protozoa thrive on carbohydrates while the author and his associates (Kagy and Faust, 1930; Faust and Kagy, 1934; Faust, Scott and Swartzwelder, 1934) demonstrated that fulminating experimental amebic colitis in dogs could be controlled with raw liver, which at times even produced cure, although liver extract introduced parenterally had no effect on the progress of the lesions or symptoms. In a few patients suffering from chronic amebiasis raw calf liver taken by mouth relieved the symptoms and in one instance produced apparent cure (Silverman and Faust, unpublished data), but the unpalatable taste of the liver made it impractical to undertake a larger clinical study These relatively isolated observations suggest that mo[illegible] extensive experimental and clinical investigations should [illegible] undertaken, with adequate controls, to determine how [illegible]

lial system, resulting in neutropenia and monocytosis. One of the serious complications is dysentery, produced not by the kala-azar organism but by *E. histolytica* or enteric bacteria. Less definite evidence of relationship is available for infections such as pulmonary tuberculosis, malaria, brucellosis, or other micro-organismal diseases, yet any disease which produces ill health may reasonably be expected to provide lowered resistance to infection with *E. histolytica*.

Summary

1. The transmission stage of *Endamoeba histolytica* from person to person is the cyst, which is passed in formed stools. The cyst is quite sensitive to drying and putrefaction but when feces are diluted with large amounts of water, these cysts will survive and retain their vitality for weeks or months.
2. Reservoir hosts, as monkeys, dogs and rats, are not considered to be important over-all sources for human infection. Man himself is primarily responsible for human amebiasis.
3. Exposure results from ingestion of viable cysts obtained from water, food and fomites. Water may be heavily polluted with cysts and produce epidemic dysentery, or it may contain only small numbers of cysts and occasionally provide chance opportunity for infection. Food may be contaminated when human feces are used as fertilizer of garden crops, more usually food is soiled by careless dirty handlers, or by filth flies and cockroaches which have mechanically transported the cysts from nightsoil to the kitchen or the table. Person-to-person infection *via* fomites is a common method of exposure in eleemosynary institutions, in unsanitated rural populations and in tropical countries.

4. Infection may result from a single large dose of cysts, producing acute infection in one or more exposed individuals; or it may be due to single or repeated doses of a small number of cysts. In hyperendemic areas many cyst passers saturate the environment with viable cysts.
5. Cysts of *E. histolytica* exhibit a wide range of infectibility and an equally wide range of virulence, although no strain of the organism has been demonstrated to be non-pathogenic. Virulence is probably enhanced by rapid passage from man to man. Size of the cyst is not an index of its pathogenicity.
6. Susceptibility to infection with *E. histolytica* is not related to race, age or sex. There is evidence that basic diets or intemperance with respect to food and alcoholic beverages may possibly contribute significantly to the complex of factors influencing susceptibility to amebiasis.
7. While antibody is produced in amebiasis, especially when deep tissue invasion occurs, immunologic reactions have not been demonstrated for any length of time after the etiologic agent has been eliminated from the body.
8. Supervening diseases undoubtedly increase susceptibility to amebiasis.

Chapter 3

Pathogenesis and Pathology of Amebiasis

COLONIZATION OF *ENDAMOEBA HISTOLYTICA*

EXPOSURE and infection in human amebiasis result from ingestion and swallowing of the viable cysts of *Endamoeba histolytica* which pass uninjured and unmodified through the stomach and proximal levels of the small intestine. The encysted organism begins to exhibit protoplasmic activity only when the gastric secretions have been neutralized or slight alkalinity has been produced by the intestinal juices (Swartzwelder, 1939). This activation and thinning of the cyst wall in the medium of the intestinal juices cause a rupture of the wall and allow the ameba to emerge as a naked protoplast (*metacyst*). Simultaneously or shortly thereafter the cytoplasm divides into a number of small amebas corresponding to the number of nuclei in the metacyst. Thus, as many as four metacystic trophozoites, possibly eight if a supernumerary division should occur, are produced from the metacyst. These little amebas (*metacystic trophozoites*) now pass down the remainder of the small intestine and are carried into the lumen of the cecum. If excystation fails to occur in transit down the small intestine, the fate of the cysts is uncertain but since excystation probably does not take place in the large bowel, the cysts may at times pass through the entire digestive tract and be evacuated in the feces, without colonization.

Once the little metacystic amebas reach the cecal area, where normally there is a moderate degree of stasis in the fecal flow, they have their first opportunity to make chance contact with the cuticular surface of the mucosa, either at the tips of the digital processes extending out from the glands, partway within the glands, or in the depth of the glands (James, 1928; Meleney, 1934; Faust, 1932, 1943). Contact, even for a brief time, allows the amebas each to digest a small cavity in the mucosal cells, in which the parasites can take harborage. They ingest the lysed material, grow, then divide by binary fission and thus initiate a colony. Perhaps tissue contact does not occur at this level of the large bowel; then the amebas will pass further down in the liquid feces, to make contact at lower levels, particularly in the sigmoid colon or rectum, where primary colonization may then develop; or they may reëncyst and be evacuated in the feces without causing infection. In a majority of exposures with small numbers of cysts it is altogether probable that this *latter is the case and that infection fails to occur.*

Although evidence preponderates in favor of the view that *E. histolytica* is characteristically a tissue invader, there is suggestive evidence that at times this ameba, like *Giardia lamblia* at the duodenal level of the small intestine, may remain temporarily as a surface-contact parasite of the mucosa, producing superficial erosion, excess production of mucus, and developing extensive colonies in the crypts (Hoare, 1950). However, whenever favorable circumstances develop tissue invasion characteristically occurs. As long as the amebas remain in the intestinal lumen it seems likely that they depend on the metabolites of certain associated enteric bacteria for growth and multiplication (Deschiens, 1937, 1938). Once they invade the intestinal mucosa these host cells appear to provide the necessary stimulus and bacteria are no longer essential.

THE UNCOMPLICATED AMEBIC LESION IN THE INTESTINE

Once an initial implantation of *E histolytica* has been made in the large bowel, the lesion develops by lytic necrosis; the colony increases in numbers at the expense of the invaded tissues and advances away from the intestinal lumen into the depth of the tissues Meleney (1934) states that the amebas are at times found on the surface of the mucosa in contact with epithelial cells which bear evidence of lytic necrosis; or they may be discovered beneath apparently intact epithelium The invasion may take place "in a depression between rugae or in the lumen of a vertical gland, or it may occur on the surface epithelium between glands." This description conforms with the observations of the author and other workers on human and experimental material (Fig. 2) Once entrance to the epithelium has been effected, the amebas may proceed along the basement membrane to the depth of the glands, or they may penetrate the interstitial tissue between the glands In both locations they advance towards the muscularis mucosae, multiplying in their course, so that the colony piles up more or less in pyramidal fashion superficial to the muscularis mucosae

Typically the sites of entry into the mucosa are discrete, minute button ulcers (Fig 3), seen with the unaided eye at autopsy as very small, edematous, reddened papillae, at times with evidence of hemorrhage, and the advancing lesions resemble the neck of a microscopic flask The invaded site may at first be quite circumscribed or by extension along the surface of the mucosa it may involve an appreciable area The histologic picture is one of necrosis, with edema if the stroma is involved. Characteristically this early lesion is remarkable because of the lack of host cell reaction, viz., lack of infiltration of neutrophilic and eosinophilic leukocytes or of macrophages



FIGURE 2 Initial contact and superficial erosion of the mucosal gland cells of the human cecum by *Endamoeba histolytica* The arrows point to two amebas initiating tissue invasion X 1600. (By permission of Colonel J E Ash and the Armed Forces Institute of Pathology.)

In many cases in which initial tissue invasion occurs the lesions are limited to the mucosal layer and only superficial ulceration develops. Frequently repair keeps pace with sloughing of the necrotic cells. Even though the glands are destroyed, replacement with basement epithelium may provide a clean protective covering for the deeper tissues (Fig. 4). If repair exceeds destruction the healing process may succeed in eradicating the

amebas from the site This type of healing process explains spontaneous "cure," which has been observed in experimental animals, a condition which is probably duplicated at times in human amebiasis

In many other instances, possibly in a majority of cases of tissue invasion, the amebas in the fundi of the glands or in the depth of the stroma eventually break through the relatively resistant muscularis mucosae into the submucosa Meleney (*l c.*) states that this penetration may occur interstitially or via the lymphatic or blood vessels In the submucous coat the amebas are able to spread out fan-wise between the connective tissue elements, producing a pattern of diffuse lytic necrosis and toxic edema (Fig 5). A section through the mucosal-submucosal tissues at this stage of development of the amebic lesion is essentially that of a bottle with a longer or shorter neck and an enlarged base It is still characteristically lacking in host-cell invasion, although a few neutrophilic polymorphonuclears and moderate numbers of monocytes may occasionally be found However, if the amebas have broken down a considerable amount of overlying mucosa, then enteric bacteria will probably have entered the necrotized tissues and round cell infiltration will have occurred



FIGURE 3 Surface of colonic mucosa of a dog experimentally infected with *Endamoeba histolytica* There are numerous, discrete, raised, "chemise button" sites, each with a minute center through which a colony of amebas has penetrated Natural size (By permission of Doctor John F Tobie)

Once the amebic process has become well established, it



FIGURE 4. Clean repair of mucosa at site of amebic ulceration of the colon of a dog experimentally infected with *Endamoeba histolytica* Note absence of round-cell and fibrocytic reaction. X 375 (By permission of Doctor John E Tobie)

tends to involve the lymphatics and blood vessels of the submucosa, with thrombosis of the latter which allows the amebas to enter the lumens of these vessels Moreover, extensive submucosal extensions frequently occur, so that adjacent subsur-

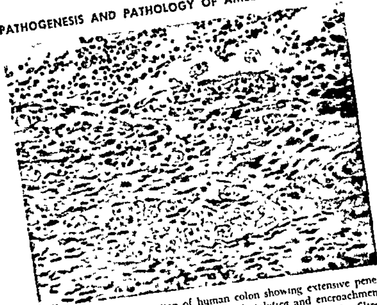


Figure 5 Transverse section of human colon showing extensive penetration of the submucosa by *Endamoeba histolytica* and encroachment on the circular muscle coat Although there is some round-cell infiltration in the damaged mucosal layer, there is essentially no host-cell reaction in the invaded underlying submucosa X 300 (In Craig's, *Amebiasis and Amebic Dysentery*, 1934, Charles C Thomas, from the Army Medical School Collection)

face lesions become joined by tunnels and superficial tissues are deprived of their blood supply, causing a sloughing of the overlying layers Likewise, peristaltic movements of the involved bowel wall squeeze out many amebas and necrotic detritus through the necks of the ulcers into the lumen of the bowel, producing partial collapse of the tissues

In fulminating amebiasis, and likewise in chronic infection but considerably less rapidly, the amebas may invade the muscular coats, then break through the barrier and reach the subserosa Meleney (1934) states that they "penetrate the muscle cells and cause edema, hyalinazation and finally necrosis of this

tissue. . . . In the subserous tissue the amebas produce edema followed by the formation of fibrin on the serous surface, which leads to adhesions of apposing peritoneal surfaces. If the necrotic process penetrates through the muscle layers, the serosa gives way and perforation occurs."

The typical uncomplicated amebic lesion which has just been described represents a relatively active process which usually produces intestinal symptoms; but occasionally many such ulcerated areas may develop without particular clinical manifestations of pathology, so that the physician is astonished by the amount of tissue destruction demonstrated at necropsy. On the other hand, at times no appreciable damage will be revealed by casual post-mortem inspection of the mucosal surface, although sections through sites of hyperemia or edema may demonstrate extensive subsurface necrosis with nests of active amebas in the eroded tissues

DEVELOPMENT OF SECONDARY INTESTINAL LESIONS

Original sites of tissue invasion and colonization by *E. histolytica* provide opportunities for development of amebic processes at other levels of the bowel and, by extension through the mesenteric lymphatics and portal blood stream, *to extra-intestinal foci* First of all it is convenient to consider the development of *secondary sites in the intestinal tract.*

Earlier in this chapter it has been suggested that the first opportunity *for development of the primary amebic lesions* is in the cecal area, since this is the first level of the bowel where any *appreciable amount of intestinal stasis occurs.* Amebic trophozoites extruded from these primary foci serve as the source for *tissue invasion at all lower levels of the bowel*, and particularly in the sigmoid colon and rectum. Moreover, additional ulcerative invasion of the cecum is likely to take place as a result of

direct contact of the extruded trophozoites with undamaged cecal mucosa, while regurgitation of these amebas into the posterior segment of the ileum allows tissue invasion of this portion of the intestine Primary implantation apparently never occurs in the wall of the ileum, nor do the amebas enter the mucosa at higher levels of the small intestine.

The development of a preponderance of primary lesions in the cecal area is a well recognized fact. Except for cases of fulminating amebic invasion throughout the entire large intestine and for a relatively small per cent of cases in which primary invasion of the lower colon and rectum occurs concomitantly with that of the cecum or exclusively in the lower segment of the large bowel, the pathologic process is characteristically a progressive one, with the earliest sites of tissue damage at the cecal level and gradual or rapid involvement at lower levels of the large bowel The cumulative lesions, as observed in autopsy findings (Clark, 1925, Faust, 1943), indicate that amebic ulceration occurs most frequently in the cecal area (cecum, appendix, ascending colon) and next in the lower portion of the sigmoid colon and rectum, while the intermediate levels of the colon are less liable to invasion (Fig 6)

CHRONIC MODIFICATION OF THE AMEBIC LESION IN THE INTESTINE

Chronic changes may develop relatively early in the infection On the mucosal surface the lesion may become a shallow weeping ulcer, possibly as extensive as a centimeter in diameter, with a hyperemic raised margin Or it may develop a diffuse granulating mucosal covering over a number of nearby invaded glands, without evidence of ulceration A third, more common early chronic type has the architecture of a raised nodule, with a sharply delimited edge and a minute, depressed, yellowish pore surrounded by a reddened ring and opening into a small

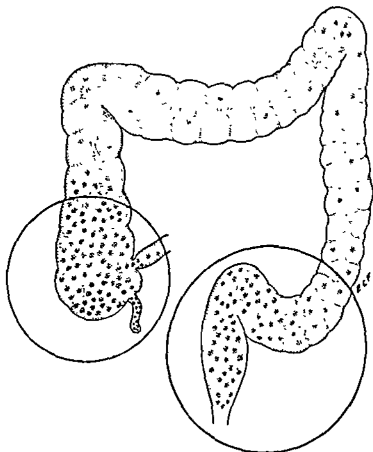


FIGURE 6 Diagram showing the relative frequency of amebic lesions at different levels of the large bowel. Note that the greatest number develops in the cecal area and the second greatest number in the sigmoidorectal area (After Faust, in *Transactions and Studies, College of Physicians of Philadelphia,* 1943)

enlarged base filled with gelatinous material, necrotic tissue and amebas

From these earlier types of chronic amebic processes extensive open ulceration may develop, with the longer diameters of separate lesions corresponding to the *transverse* plane of the intestine. The edges of these ulcers become raised, thickened and overhanging, at times with extensive cicatricial binding and projection into the intestinal lumen. Histologically these edges consist of a matrix of fibrous tissue, while the underlying cellular components are made up of a dense infiltrate of neutrophilic leukocytes extending into the submucous or muscular coats and at times providing a relatively compact wall around the margins of the necrotic base This advanced picture has resulted from the invasion of enteric bacteria into the amebic lesion, providing the stimulus for host-cell infiltration, a complication seldom present in the earlier amebic lesion (Fig 7). Finally, extensive areas of sloughing may occur, due to cutting off the underlying blood supply At times even necrotic elements of muscle tissue are discharged in the sloughed tags. Repair of the more advanced lesions commonly leads to cicatricial thickening of the involved portion of the intestinal wall, with more or less permanent loss of normal architecture and function In chronic intestinal amebiasis repair may proceed at one level while at the same time active destruction of tissues is taking place at another

COMPLICATIONS OF INTESTINAL AMEBIASIS

Appendicitis Ochsner and De Bakey (1942) state that an acute or chronic inflammatory process of the appendix is one of the most frequent complications of amebiasis Suppurative appendicitis is present in 7 to 40 per cent of fatal cases of this disease The manifestation may mimic acute appendicitis so closely that only the awareness of amebic etiology and recovery

of the amebas will prevent hasty operative intervention (Howell and Knoll, 1941). In the Tulane University Surgical Service routine stool examination by the author's laboratory has demonstrated that 10 per cent of patients having a tenta-



FIGURE 7 Transverse section through the human colon, showing a characteristically enlarged, flask-shaped amebic ulcer in chronic amebic colitis There is complete destruction of mucous and submucous layers within the lesion, which is occupied by cytolyzed necrotic débris Adjacent tissue is protected by a dense layer of round cells which have walled off the ulcer. X 75 (In Craig's, *Amebiasis and Amebic Dysentery*, Charles C Thomas, 1934, from the Army Medical School Collection.)

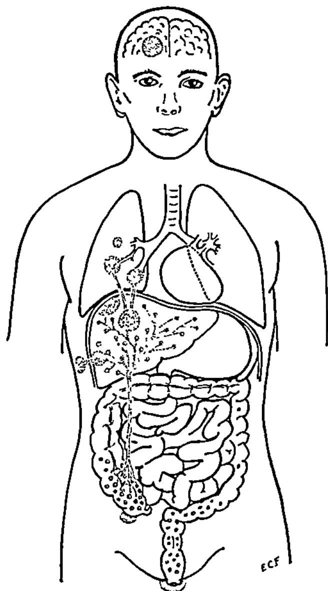
tive diagnosis of chronic appendicitis were actually suffering from amebiasis of the cecal-appendiceal area. Anatomically, the lesions may be in the wall of the appendix, cecum, adjacent segment of the ascending colon, or on the margins of the ileocecal valve. Pathologically, they do not differ fundamentally from

the chronic type of ulceration produced by *E. histolytica* in other sites of the large bowel

Perforation of the intestinal wall. This may occur in relatively quiescent cases of intestinal amebiasis in which the amebic lesion progresses much more extensively beneath the surface of the mucosa than superficial appearance of the wall would suggest In the acute dysenteric type perforation is much more rapid and more frequent the colon, as seen proctoscopically or at autopsy may be paper-thin with numerous perforations, or thickened with granulomatous perforations (Armstrong, Wilmot and Elsdon-Dew, 1949) Armstrong, Elsdon-Dew and Marot (1949) state that 10 per cent of the approximately 2,500 Africans entering King Edward VIII Hospital in Durban, Natal with fulminating amebic dysentery died from perforation and collapse In many instances perforation, with release of the enteric bacteria into the peritoneal cavity, proceeds to peritonitis, although mesenteric adhesions may develop and prevent extensive sepsis

Massive hemorrhage This complication develops occasionally as a result of erosion through the walls of mesenteric blood vessels over relatively extensive areas of deep amebic ulceration of the colon (Strong, 1901, Craig, 1944)

Amebic granuloma Most of the recent clinical investigators refer to this complication under the designation of "*ameboma*" The lesion is a tumor mass, relatively firm and nodular, with a fibrous outer wall and one or more internal "abscesses" which contain necrotic tissue elements and amebic trophozoites Although amebomas may develop at any site along the length of the large intestine, Niño (1942) found that they have a predilection for the cecum (34 per cent), the transverse colon (17 per cent) and sigmoid colon (14 per cent) The cut surface of the tumor reveals an outer covering of edematous, ulcerated mucosa, infiltrated with fibrous tissue which frequently fixes the mass to adjacent portions of the intestinal wall Immediately



(see legend on following page)

within there is a zone of granulation, characterized by round-cell infiltration, many eosinophils (not observed in uncomplicated amebic colitis), lymphoid hyperplasia and a few fibroblasts. The core of the tumor contains necrotic tissue cells and amebic trophozoites. Although amebomas may superficially resemble tubercular abscesses, carcinoma, actinomycomas and other tumor-like growths in the intestinal wall, the histologic structure is specifically distinctive.

EXTRA-INTESTINAL AMEBIASIS

Amebiasis outside the intestinal tract is invariably secondary to amebic invasion of the large bowel. The anatomical locations where extra-intestinal amebic lesions have been demonstrated include practically all soft organs and tissues, of which the liver, lungs, brain and skin are most commonly involved. (See diagram, Fig. 8.)

HEPATIC AMEBIASIS

This includes three types: (1) hepatitis associated with colonic amebiasis but without evidence that amebic invasion of

FIGURE 8. Diagram showing (1) *important primary foci of amebic lesions* in the large intestine (cecal and sigmoido-rectal areas), and (2) *the more common secondary extra-intestinal sites*, resulting from direct or hematogenous extension from the intestine. These latter locations, in order of frequency, are: (a) *hepatic* (multiple miscroscopic implantations producing hepatitis, and, later, one or at most a few abscesses, usually in the upper portion of the right lobe of the liver), (b) *pleuro-pulmonary* (commonly by direct extension of an hepatic abscess through the diaphragm into the pulmonic parenchyma, into a bronchus, or into the pleural cavity, rarely by the hematogenous route from the intestine to the lungs), (c) *cerebral* or rarely cerebellar (by the hematogenous route from the liver, lungs or colon), (d) *peritoneal*, and (e) *cutaneous* (usually perianal as a complication of amebic colitis, or from rupture of a liver abscess through the body wall). (Original adaptation.)

the liver has occurred, (2) acute amebic hepatitis; and (3) amebic liver abscess.

Loeber and D'Antoni (1947) first called attention to an enlarged tender liver in children suffering from colonic amebiasis but without any of the usual clinical signs of hepatic involvement in amebiasis, such as leukocytosis, fever and x-ray evidence of diaphragmatic impairment. Sodeman (1950a) refers to this condition as "a lower grade hepatic process" (that occurs) "before the stage of acute hepatitis" . . . "with enlargement or tenderness of the liver but very little in the way of systemic response" The histopathologic picture in this type of hepatitis has not been reported

Acute amebic hepatitis. This is the stage of amebic invasion and colonization of the liver preceding development of one or more abscesses In order to understand the pathogenesis of amebic hepatitis, it will be helpful to refer again to the amebic lesions in the intestine, particularly those in the cecal area. Lytic necrosis in the submucosal layer involves not only the interstitial cells but the mesenteric blood vessels as well. Frequently the walls of the mesenteric venules are eroded to such an extent that amebas gain entrance to these vessels and are carried into the intra-hepatic portal vessel. Yet only a small proportion (not over 5 per cent) of persons with confirmed amebic colitis have evidence of coincident or subsequent amebic hepatitis

It is generally accepted by pathologists and clinicians that *E. histolytica* enters the liver via the portal blood stream. The recent study of Carrera (1950) on hepatic amebiasis following experimental development of amebic colitis in kittens confirms the findings of Rogers (1922) and Palmer (1938) on human material, namely that the earliest colonization of the amebas is associated with thrombosis in branches of the portal vein, and particularly in the small interlobular veins. The thrombi are composed of fibrinous filaments and leukocytes, usually in close contact with the amebas The lytic properties of the amebas to-

gether with the occlusion of the vein cause necrosis of the wall of the vessel, so that some amebas work their way into periportal sinusoids and extend necrotic pathways into the lobule, at times involving the central or collecting vein in this erosive process. In its earliest stage of development the lesion is usually relatively free of inflammatory reaction but as soon as necrosis becomes extensive infiltration of large numbers of neutrophilic leukocytes characteristically takes place, possibly, as Carrera (*l c*) has suggested, in response to the necrotic host tissue itself At this stage there is no evidence of fibroblastic repair The initial hepatic lesion probably does not require a preliminary or concomitant invasion of the liver by enteric bacteria This conclusion is substantiated by the fact that a majority of the early amebic lesions and even amebic abscesses of the liver are bacteriologically sterile

Acute amebic hepatitis may consist of a single site of colonization of the organisms, or of multiple sites (Meleney, 1934). The latter would produce more areas of necrosis, and would therefore be expected to cause a more rapid generalized hepatitis Nevertheless, both clinical and autopsy observations indicate that only one, or at most relatively few of these sites progress to abscess formation

Amebic liver abscess No absolute demarkation can be made between the termination of amebic hepatitis and the beginning of amebic liver abscess, since the latter is merely a radial extension of the lytic necrosis of hepatic cells by the amebas in one or more sites, the centers of which come to be filled with a purée of necrotic débris The smallest abscesses, to quote Meleney (*l c.*), "may be only a few millimeters in diameter They are solid and white and still show some semblance of liver structure In slightly larger ones the contents are gelatinous and yellow, and still larger ones contain a reddish brown fluid and shreds of necrotic tissue" If development of the abscess has been rapid, there has not been opportunity for development of a fibrous

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capsule, but in the chronic process there is usually a limiting wall.

Microscopically, there are three recognizable zones in the active abscess, viz., (1) the outermost zone of relatively normal tissue which is in the state of being invaded by the amebas; (2) a median zone in which the vital tissues have been destroyed and only the stroma remains; and (3) the necrotic center.

Single abscesses are more commonly encountered in cases which are seen clinically; multiple abscesses are more frequently found at the autopsy table (Craig, 1944). A majority of single abscesses develop in the right lobe of the liver, either just below the diaphragm or at the lower aspect near the surface. The solitary ones may be as large as a grapefruit, with trabeculated strands of more resistant stroma. Ash and Spitz (1945) state that more than 50 per cent of these abscesses involve the diaphragm, and usually rupture into the lung, but some rupture into the colon, while a small percentage rupture into the peritoneal cavity and occasionally one ruptures through the abdominal wall, or even into the gallbladder

PLEUROPULMONARY AMEBIASIS

The pleura and lungs constitute the second most common and most important extra-intestinal locations of amebiasis. There are several demonstrated ways whereby these organs and tissues may become involved: (1) from the intestine via the blood stream or mesenteric lymphatics and inferior vena cava, without hepatic involvement; (2) by concomitant but independent involvement of liver and lungs; (3) with pulmonary extension of an hepatic abscess; (4) due to a broncho-hepatic fistula with pulmonary involvement; and (5) by empyemal extension from an hepatic abscess According to Ochsner and De Bakey (1936) the respective percentage incidences of these five varieties of pleuropulmonary amebiasis are: 14.3, 10.4, 37.2,

19 6 and 15 6. Thus it is evident that in most cases pleuropulmonary involvement is an extension of hepatic amebiasis However, amebiasis of the pleural cavity is only about 5 to 10 per cent as frequent as hepatic involvement

In the pleuropulmonary extension of an hepatic lesion, the typical mechanism involves the doming up of the diaphragm above a subdiaphragmatic abscess of the right lobe of the liver, adhesion of the lower lobe of the right lung to the diaphragm, lytic penetration through the tissues of the diaphragm and erosion by the amebic process directly into the lung Here localized pneumonitis develops, with formation of an abscess containing a gelatinous menstruum containing erythrocytes, large mononuclear cells from the walls of the alveoli, amebic trophozoites and undigested elastic tissue elements (Meleney, 1934) There is usually a fistulous opening into a large bronchiole or bronchus, so that the reddish-brown contents of the pulmonary abscess, and at times of the hepatic abscess, are coughed up and discharged In case the amebas have arrived in the lung by the blood stream, the diaphragm is not involved and the pulmonary abscess at first lies wholly within the parenchyma of the lung. Rarely there is more than one such abscess

CEREBRAL AMEBIASIS

Amebiasis of the brain is very uncommon compared with hepatic and pleuropulmonary infection Izar (1932) found 56 records of cerebral amebiasis in the literature, of which 29 were from Egypt Huard (1937) collected a total of 59 cases. Although inoculation is considered to be exclusively hematogenous in origin, with rare exceptions brain involvement is associated with hepatic or pleuropulmonary amebiasis, most frequently as a metastasis from the lungs (Ochsner and De Bakey, 1942). An exception is the case which came to autopsy in the Charity Hospital of Louisiana, New Orleans, August, 1947

(Swartzwelder and McGill, 1949). Living *Endamoeba histolytica* were recovered from a solitary brain abscess and have been continued in culture by the author and his associates since that time (Tulane strain No 22, which has proved to be highly pathogenic for experimental animals). In this case primary lesions were found in the colon but there was no evidence of hepatic or pleuropulmonary amebiasis.

Macroscopically, the affected area of the amebic brain appears edematous and congested. The outer wall of the abscess is thin, its inner aspect is fuzzy and the contents consist of a purée of reddish-brown, pinkish or light grayish color. The brain abscess is characteristically sterile with respect to bacteria. Microscopically, there is at first a congestion and thrombosis of the blood capillaries in contiguous tissue, while nearby there are amebas which have escaped from these vessels into brain tissue that is beginning to show evidence of lytic necrosis. From such an initial lesion an abscess proceeds to develop, with degenerate tissue cells, erythrocytes and leukocytes in the cavity, and in the inner portion of the wall many lymphoid cells, degenerate nerve cells and amebic trophozoites.

CUTANEOUS AMEBIASIS

The skin is the fourth most common anatomical location outside the large bowel for development of *Endamoeba histolytica* Cutaneous amebiasis may develop (1) from drainage of an amebic liver abscess, following spontaneous rupture or surgical intervention; (2) from drainage of an appendiceal or colonic lesion, (3) as a perianal extension of amebiasis of the colon; or (4) without definite evidence of previous visceral amebiasis (Engman and Meleney, 1931). Altogether considerably less than 100 proven cases of amebiasis cutis have been reported. Grossly there is edematous elevation of the involved skin, with induration of the margin of the developing ulcer. The char-

acteristic features of this lesion include: a rapidly spreading ulcerative process of irregular margins, with an overhanging ledge of gangrenous epidermis, and an advancing zone peripheral to the ulcer, which has a dusky red hue and gradually merges with normal skin. The ulcer itself contains a blood-tinged exudate of fetid odor and has a base of dirty-grayish necrotic tissue, in which motile amebas are to be found advancing into the peripheral zone.

AMEBIASIS IN OTHER EXTRA-INTESTINAL SITES

Rarely, as a result of hematogenous or direct extension of intestinal or hepatic amebiasis, amebic involvement has been found to occur in the spleen, epididymis, testis, prostate, penis, fimbriated tubules, ovaries, cervix and vagina (Ochsner and De Bakey, 1942, Craig, 1944).

Summary

1 Primary infection with *Endamoeba histolytica* results from the ingestion of viable cysts of this organism, from which the naked metacyst escapes in the medium of neutral or slightly alkaline juices of the small intestine. The organism divides into a number of tiny metacystic trophozoites corresponding to the nuclei of the metacyst. These pass down in the fecal current through the ileocecal valve into the cecum.

2 By chance contact with the mucosal cells at the cecal level, and to a lesser extent at more distal levels of the large intestine, each ameba digests a little pocket, grows, multiplies and initiates tissue invasion. At times these amebas may possibly establish themselves temporarily in the glandular crypts, living on mucous secretions or producing only superficial erosion of the mucosal cells.

3. Once tissue invasion has begun at a pinpoint site on the *surface of the mucosa, invasion characteristically proceeds* as a narrow erosive column to the base of the mucosa, causing lytic necrosis of the epithelial cells.
4. In some instances the lesion does not extend below the mucosa and repair takes place as rapidly as the tissue is *destroyed Probably much more frequently the muscularis* mucosae is penetrated and the colony of amebas digests its way into the submucosa to develop an enlarged necrosing pocket. This is the characteristic uncomplicated amebic ulcer, with pinpoint entry into the mucosa, an advancing *neck to the muscularis mucosae and an enlarged* submucosal base. At times the lesion continues into the muscular coats and occasionally may reach the subserosa or may perforate into the peritoneal cavity.
5. The most common sites for primary ulceration are in the cecal area (cecum, appendix, adjacent portion of the ascending colon), next is the sigmoidal-rectal area. Progeny are extruded from these ulcers into the lumen of the large intestine and may initiate multiple secondary lesions in the intestinal wall, particularly at lower levels but occasionally following regurgitation, in the terminal ileum. Likewise, by erosion of mesenteric venules they may enter the blood stream and become lodged in the smaller blood vessels of the liver or other organs where they may produce one or more minute sites of erosion. Occasionally these develop into so-called abscesses.
6. Uncomplicated amebic lesions in the intestine call forth essentially no host cell response.
7. Undermining communications between pockets of amebas in the submucosa cut off the blood supply, causing gangrene and sloughs of the overlying layers. Enteric bacteria characteristically enter these larger pockets and provoke extensive *neutrophilic and fibrocytic infiltration of*

the wall of the ulcer. This is the picture in the more chronic stage of the lesion.

8 Complications of intestinal amebiasis include acute or subacute appendicitis, perforation, rarely massive hemorrhage from the wall, and at times amebic granulomas (amebomas).

9 The most common site of extra-intestinal amebiasis is in the liver At first the lesion is a minute one in the smaller portal radicles, at one or more foci where fibrin and leukocytes produce embolic blockage. This is an acute inflammatory process, characteristically bacteria-free, with colonization of amebas which extend the lesion into the hepatic sinuses. One or more of these lesions may proceed to abscess formation These abscesses develop most frequently on the upper aspect of the right lobe of the liver.

10. Pleuropulmonary invasion by the amebas usually occurs as an extension of an hepatic abscess through the diaphragm into the lower extremity of the right lung, but rarely pulmonary infection may take place by the hematogenous route directly from the intestinal wall

11. Less frequently foci of amebas are located in the brain, spleen, urinary and genital organs. These lesions are invariably secondary to intestinal amebiasis.

12. Amebiasis cutis is an uncommon complication which usually develops following rupture of an amebic liver abscess through the abdominal wall or as an extension of rectal amebiasis.

Chapter 4

Manifestations and Clinical Evidences of Amebiasis

THE patient who presents himself to a physician for advice and care may have had a recent attack of acute diarrhea or dysentery, recurrent bouts of colitis, or chronic colitis He may be suffering from pain in the region of the appendix, with or without loose bowel movements, or may complain of general abdominal distress with anorexia and lack of appetite. He may be disturbed by fullness and pain in the right upper abdominal quadrant He may have no well-defined subjective symptoms but feels exhausted and below par. Or he may be requesting a routine health examination, unaware of any difficulty. All of these types of patient-physician contact provide opportunity for awareness of amebiasis. Shattuck (1951, p. 583) has remarked: "There is no syndrome or clinical picture characteristic of the infection and the symptoms and signs may simulate a great variety of other diseases"

It is important, in fact essential, for the physician in general practice as well as the specialist in gastroenterology to have a basic understanding of the underlying etiology and pathogenesis of amebiasis, together with knowledge of appropriate technical procedures for making accurate differential diagnosis. In this connection it should be remembered that in a large pro-

portion of cases specific diagnosis of amebiasis originates in a consciousness that this infection is a possible cause of the symptoms and signs elicited Thus, in a potential diagnosis of amebiasis, as in all other diseases, responsibility for recognition rests primarily with the physician into whose care the patient places himself

CLINICAL CLASSIFICATION OF AMEBIASIS

For practical purposes amebiasis may be divided into two major subdivisions, viz , intestinal and extra-intestinal. Primary infection involves only the large intestine while extra-intestinal infection is invariably secondary to original infection in the large bowel. Until about three decades ago there were only two clinically recognized manifestations of amebiasis, i e., amebic dysentery and amebic liver abscess, but, as the manifold symptoms of this infection became better understood and appreciated, there was gradual realization that these two clinical entities constituted only small segments of the entire picture. A modern, widely accepted classification may be outlined as follows

A *Intestinal Amebiasis*
  1 Acute or chronic dysentery or diarrhea
  2 Appendiceal syndrome
  3 Asyndromic infection
  4 Asymptomatic infection, existing in so-called "healthy carriers"
  5 Complications

B *Extra-intestinal Amebiasis*
  1 Hepatic amebiasis
    a. Amebic hepatitis
    b Amebic liver abscess
  2 Amebiasis of other viscera (pleuropulmonary involvement, brain, genital organs, etc.)

abdominal cramps, at times nausea and vomiting, and an urgent sense of a need to defecate. In a much larger number of infected individuals there may be a long period of vague abdominal discomfort preceding an acute attack, or there may be only an undefined history of malaise, loss of appetite and weight, without a frank attack of colitis Again, colonic infection may produce no detectable symptoms and the first suggestive evidence of amebic infection may be acute hepatitis Finally, in many individuals with intestinal amebiasis there may be no clinically discoverable evidence of the infection. In this connection, Craig (1944) has pointed out that "cases with grave intestinal lesions may sometimes come to autopsy in which the individuals during life had no intestinal symptoms sufficiently prominent to attract attention."

INTESTINAL AMEBIASIS

Dysentery or diarrhea. Dysentery is basically a pathologic term indicating irritation of the wall of the intestine, sufficient to produce symptoms of abdominal pain with relatively frequent discharge of fecal material accompanied by blood and mucus The feces may be either formed, soft or liquid in consistency Diarrhea connotes a condition of unformed feces, resulting from their rapid passage through the lower levels of the colon without normal dehydration. Bloody diarrhea is one form of dysentery

In fulminating cases of *amebic dysentery* at times there may be an excess of blood, mucus and tissue detritus but the stool typically contains considerable feces. In contrast, in *acute shigellous there is characteristically* an excess of mucus, tissue cells, frequently less blood and at times no macroscopic fecal material It is helpful to keep these concepts in mind in considering a clinical diagnosis of amebic colitis, since much laxity has prevailed in the use of these several terms. For example,

Napier (1946, page 425) employs the term "amebic dysentery" for all primary manifestations of intestinal amebiasis, regarding non-dysenteric infections "as complications, or sequelae of the primary infection of the bowel wall, which may have been sub-clinical." This is the older, outmoded idea of colonic amebiasis which in some respects is self-contradictory. Moreover, it fails to recognize modern experience in the field of amebiasis

Acute amebic dysentery, at least in its primary attack, varies remarkably in degree, from one of intense severity with evacuation of considerable amounts of blood, mucus and sloughed tissue tags to milder types in which evidence of hemorrhage and tissue destruction is much less pronounced The fulminant type is observed more frequently in tropical and subtropical countries where environmental conditions are often conducive to heavy exposure; the milder type is more characteristic of temperate zones Yet these distinctions are only relative in their geographic application

The acute attack may be preceded by one or more days of diarrhea, with abdominal distress, or it may be precipitated without warning. Occasionally amebic ulceration involves practically the entire large bowel, in which tissue destruction and hemorrhage occur at multiple sites from the ileocecal valve through the rectum Frank dysentery also develops from lesions exclusively in the sigmoid colon and rectum Tenesmus is more pronounced if these latter levels are affected and is moderate or at times essentially lacking if no lesions are discovered at proctoscopy. The initial dysenteric episode typically does not produce marked prostration or fever

An acute attack of dysentery may terminate rapidly or subside slowly Rarely it may become so fulminant as to cause perforation of the intestinal wall and end fatally in spite of skilled clinical intervention Repeated attacks may be separated by close or prolonged intervals, during which acute symptoms

subside and the stool may become formed or even constipated, with little or no macroscopic evidence of blood. In case of frequent episodes of severe dysentery, moderate to severe prostration is experienced, dehydration occurs as a result of water loss in the stools, emaciation develops and anemia results from uncompensated blood loss through intestinal hemorrhages. Fever in intestinal amebiasis suggests bacterial invasion of amebic lesions or possibly metastasis of the amebic process to extra-intestinal locations.

The longer the infection persists, the greater will be the amount of irreversible damage to the intestinal wall Moreover, primary foci originally confined to the cecal-appendiceal area will provide amebic progeny for additional lesions at lower levels of the bowel, as well as for potential invasion of the liver and other extra-intestinal organs. These facts provide background information explaining how acute dysentery becomes transformed into chronic amebic colitis, or may be responsible for initiation of new foci for subsequent acute attacks.

Amebic diarrhea may be acute or less severe in degree. It denotes irritability of the mucosa at some level of the large intes- [illegible] peristalsis in the

[illegible]

place Probably a majority of amebic [illegible] diarrhea without macroscopic blood are situated in the cecum and in the upper levels of the colon. There may be considerable mucus mixed with the feces, sometimes microscopic elements of tissue débris, red blood cells and active amebas; or there may be no evidence of abnormality except the diarrheic consistency of the stool Mild diarrhea may be a prodrome to a dysenteric episode, may span intervals between more acute diarrheal attacks, or may continue on an even course for long periods of time.

In case amebic colitis has persisted for years, with a history of severe or mild involvement, termination of the infection by

specific chemotherapy may leave the colon seriously impaired architecturally and functionally, so that henceforth only unformed stools will be passed.

Chronic amebic colitis once developed may persist for 30 to 40 years (Strong, 1944), with or without acute exacerbations.

Appendiceal syndrome. One of the most important and helpful clinical developments in recent years with respect to intestinal amebiasis concerns amebic infection of the cecal area (Faust, 1943) Postmortem studies by Clark (1925) and experimental work by numerous investigators, amply substantiated by clinical experience, have shown that a majority of primary amebic lesions develop in the cecal area, viz., cecum, appendix and adjacent portion of the ascending colon These sites of infection may, and frequently do, produce symptoms simulating acute, subacute or chronic appendicitis, irrespective of whether the lesions are in the appendix itself or are in adjacent levels of the intestine.

The symptoms may be very acute, with sudden onset, stabbing pain in the region of the appendix, tenderness and rigidity over McBurney's point, chilly sensation, elevation of temperature and a leukocytosis—all suggestive of acute appendicitis More often the development of symptoms is relatively insidious, with constant or intermittent dull pain, moderate tenderness and muscular rigidity over the appendix, moderate leukocytosis and rarely slight elevation in temperature. Again, severe nausea and vomiting may suggest peptic ulcer or cholecystitis. If the ulceration is extensive and hemorrhage is severe, dysenteric stools may be passed. More frequently there will be intermittent diarrhea at the time of more pronounced symptoms, alternating with apparently normal or constipated stools In a majority of instances a single sample of the stool may furnish no gross evidence for suspicion of amebiasis

The particular need for considering amebiasis when an appendiceal syndrome exists is the danger of surgical intervention

in the presence of amebic ulceration of the cecal area Craig (1944) states that 3.4 per cent of the cases in the Chicago epidemic of amebiasis in 1933 were diagnosed clinically as appendicitis and that these constituted 17.1 per cent of all the fatal cases. Moreover, appendectomy in the presence of amebic ulceration in the line of incision has been found to prevent healing of the sutured tissue (Ochsner and De Bakey, 1939). Except in emergencies the possibility of amebic etiology of appendicitis should be carefully explored before surgery is decided upon If amebiasis is demonstrated, anti-amebic therapy should first be administered. In many cases this will produce cure and obviate the need for surgery (Ochsner and De Bakey, *l c.*).

Asyndromic infection. *This form of amebiasis probably* exists in a majority of infected individuals who do not exhibit the more dramatic symptoms previously discussed under the topics of amebic dysentery, amebic diarrhea and the appendiceal syndrome For lack of careful clinical study these cases have frequently been considered as "symptomless" Because there are no distinctive symptoms the patients themselves are at times *not aware that they are physically and physiologically* subnormal. Paterson (1935) has sized up this group as follows: "Because these individuals do not complain of symptoms it by no means follows that they are free from pathological lesions. *Endamoeba histolytica* lives at the expense of its host, and therefore some degree of ulceration of the intestinal mucous membrane is always present."

Symptoms of an asyndromic nature which should lead to a possible suspicion of intestinal amebiasis include: (1) evanescent diarrhea frequently alternating with constipation; mild colicky pain in the lower quadrants of the abdomen, frequently with flatus; excessive or decreased appetite, and moderate anorexia or nausea, (2) slight headache, usually *of frontal* type; neuralgic or myalgic disturbances of the back and ex-

tremities, particularly on awakening in the morning; drowsiness and mental fatigue, reduced intellectual alertness, mental depression or irritability, and (3) easy fatiguability and general malaise

Craig (1934) has analyzed these symptoms in considerable detail Constipation in the asyndromic patient is frequent, with an irregular copious bowel movement, at times followed at a short interval by an unformed stool, then a constipated state for several days before defecation again occurs Abdominal fullness and moderate discomfort, with flatulence and gaseous eructation, typically accompany the period of constipation but complete relief is characteristically experienced on discharge of the feces The periods of mild diarrhea are short and are never as pronounced as the constipated condition It must be remembered, however, that many patients with amebiasis have no history of constipation or diarrhea In some individuals the most notable symptoms are referable to a capricious appetite, with excessive hunger, or anorexia and nausea associated with the sight or even thought of food Loss of weight is at times the most concrete symptom, occurring characteristically in hot weather Neurologic and psychic disturbances mentioned in the preceding paragraph are more difficult to associate causally with amebic infection but relief from these symptoms following accurate diagnosis and adequate anti-amebic treatment provides evidence of this relationship Disturbances of the circulation and the heat-regulatory mechanism, especially in the skin, likewise require careful analysis with respect to amebic etiology

Asymptomatic Infection The majority of so-called "healthy carriers" have been placed in this category as a result of insufficient clinical study, since many of them belong in the asyndromic group Nevertheless there are cases in which no subjective evidence of infection can be elicited and in which objective evidence consists solely of recovery of the cysts of *Endamoeba histolytica* consistently or periodically in the feces.

children with amebic colitis Loeber and D'Antoni (*l.c.*) reported tender, enlarged liver, disturbances in appetite and habits of defecation, personality difficulties, a "fading suntan" dermatitis and at times a mild pyrexia. These hepatic findings need considerably more clinical study before they can be critically appraised

Acute amebic hepatitis. The pathologic basis of this condition has been considered in Chapter 3. In this type of hepatic amebiasis chills, fever and neutrophilic leukocytosis are concomitant findings with an enlarged tender liver. There is as yet no bulging of the liver although there may be some diaphragmatic impairment. There may or may not be a history of previous or current diarrhea or dysentery. Jaundice is not common. Sodeman (1950b) states that liver function tests are not particularly helpful, since the amebic lesions at this stage have produced comparatively little hepatic dysfunction This situation is the precise reverse of that seen in infectious hepatitis, and that due to leptospirosis or relapsing fever, in which the laboratory tests are usually more revealing than the physical findings.

Amebic hepatitis invariably precedes amebic liver abscess The former almost always responds to chloroquine or emetine therapy, while the latter will frequently require not only specific anti-amebic therapy but aspiration of the necrotic material from the center of the abscess before symptoms are relieved Hence there is definite need to apprehend the infection in the earlier stage (De Bakey and Ochsner, 1951).

Amebic liver abscess. This is the culmination of the amebic process in the liver. The infarction in the intrahepatic portal venules and lytic necrosis have proceeded to a stage in one or more foci in which extensive local damage has been produced. In addition to the clinical findings characteristic of acute amebic hepatitis the x-ray or fluoroscopic picture usually reveals an enlargement on one face of the liver (Figs. 9, 10),

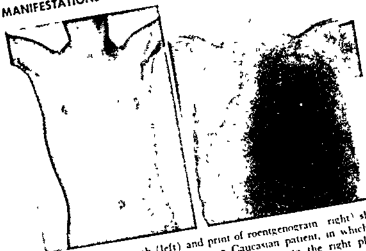


FIGURE 9 Photograph (left) and print of roentgenogram (right) showing amebic abscess of the liver in a Caucasian patient, in which the abscess had ruptured through the diaphragm into the right pleural cavity. The right side of the chest shows a bulging enlargement. The reproduction of the x-ray is reversed. (From Chen, Van Gorder and Yuan, Dept. of Surgery, Peking Union Medical College, 1931.)

although at times the abscess may be buried deeply in the organ. In a series of 1,609 cases which Ochsner and De Bakey (1939) collected from the literature, 65.1 per cent had a single focus. In their own series of 99 cases these investigators had 87.8 per cent solitary abscesses. The right lobe was involved in 84.4 and 95.9 per cent respectively of these two series.

Upper right abdominal pain, associated with a developing abscess in this area, is the most conspicuous single symptom (Ochsner and De Bakey, *l.c.*). In addition to the enlarged area and the signs relatively pathognomonic of acute amebic hepatitis, liver abscess patients are weak and underweight, probably resulting from systemic intoxication due to the necrotic tissues within the abscess pockets. Diarrhea, nausea and vomiting, and jaundice are less frequently observed.

Amebic liver abscess is much more common in the male than in the female (95.3 per *cent males in the series collected by* Ochsner and De Bakey, *l.c.* from the literature and 85.4 per cent *males in their own series*). The age frequency extends from infancy to the later decades of life but the bulk of the



FIGURE 10 Photograph (left) and print of roentgenogram (right) of amebic abscess of the liver in a Chinese patient, in which the abscess had spontaneously ruptured through the lateral wall of the chest. The reproduction of the x-ray is reversed (From Chen, Van Gorder and Yuan, Dept of Surgery, Peking Union Medical College, 1931.)

cases lie between 30 and 50 years of age (Ludlow, 1926; *Rogers and Megaw, 1935; Ochsner and De Bakey, 1939*).

A great majority of amebic liver abscesses are bacteriologically *sterile*. The average differential white count correspondingly shows only a moderate increase in neutrophilic leukocytes, *even though the total white count averages* approximately twice that of normal. Any remarkable increase in neutrophiles in liver abscesses definitely suggests pyogenic involvement.

PLEUROPULMONARY INVOLVEMENT

The clinical manifestations of amebiasis of the lungs and pleura differ according to the route of invasion and the massiveness of the lesion. In the most common type, viz., an extension of amebic liver abscess through the diaphragm, the predominant symptom is usually intense pain in the lower right side of the chest, as a result of inflammation of the diaphragmatic pleura. Next is a persistent unproductive cough. If the advancing process breaks through into a bronchus there is characteristically a large amount of pinkish-yellow- or chocolate-colored sauce coughed up. In case any considerable volume of pulmonary tissue is involved there will be evidence of dyspnea. In most cases there will be an enlarged tender liver, a low grade pyrexia, leukocyte count somewhat greater than in amebic liver abscess, and x-ray demonstration of "a triangular shadow with the base toward the liver and the apex extending toward the hilum" (Ochsner and De Bakey, 1939).

AMEBIASIS OF THE BRAIN

This is usually an extension of hepatic or hepato-pleuropulmonary amebiasis via the blood stream. However, isolated instances are known in which primary amebiasis in the colon is followed solely by a secondary lesion in the brain (Swartzwelder and McGill, 1949). Cerebral amebiasis is a fulminating process, invariably terminating fatally in a week to 10 days. Izar (1932) has reported the anatomical sites of 45 cases as follows: 12 single abscesses in the right hemisphere, 10 in the left hemisphere, six bilateral, six opening into a lateral ventricle, one cerebellar and 10 undetermined.

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FIGURE 10 Photograph (left) and print of roentgenogram (right) of [illegible] had [illegible] repro- [illegible] Yuan, [illegible]

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AMEBIASIS OF OTHER VISCERA

Amebiasis of the spleen and gall gladder is typically an extension of an amebic lesion in the liver, but splenic amebiasis may develop through blood vessels directly from the colon. Amebic cystitis and nephritis have been reported in the literature, likewise amebic orchitis, epididymitis, salpingitis, vaginitis, cervicitis, and ovaritis. All of these anatomical types are rare (Huard, 1937). They are believed to be direct extensions from amebiasis of the colon or liver.

AMEBIASIS CUTIS

This site of involvement results almost always from accidental infection following rupture or drainage of an amebic liver abscess, or as a direct perianal extension of amebic infection in the terminal portion of the rectum. Clinical evidence consists in observing the development of a swollen area of the skin with elevated hardened margins, peripheral dark-red pigmentation, and undermining necrosis giving rise to an open ulcer with a dirty grayish floor and a blood-tinged exudate of fetid odor (De Bakey and Oschner, 1948).

Summary

1. Amebiasis is protean in its clinical expression.
2. The clinical incubation period may occasionally be as short as four or five days, more frequently it averages nine days to a month, and it may be as long as one year. In most patients it is not possible to ascertain with certainty the period between exposure and the first appearance of symptoms.
3. The onset of intestinal amebiasis may be sudden but more frequently it is insidious.
4. Intestinal amebiasis may be acute and fulminant, with manifestations of frank dysentery or diarrhea. It may produce a syndrome of appendicitis, peptic ulcer or gall-bladder disease, particularly when the ulcers are primarily or exclusively in the cecal area. Again, the manifestations may be asyndromic, with or without notable abdominal discomfort. Finally, there may be no clinical evidence of disease.
5. Uncomplicated intestinal amebiasis characteristically causes no appreciable fever and no remarkable leukocytosis. If these manifestations occur in the course of intestinal amebiasis, there is suggestive evidence of bacterial or other etiologic complications.
6. Amebic hepatitis is relatively syndromic: there is an enlarged tender liver, a moderate neutrophilic leukocytosis and a moderate elevation of temperature. Amebic liver abscess is characterized by an increase in these symptoms, usually with x-ray evidence of a doming up of the right lobe of the liver against the diaphragm.
7. Pleuropulmonary amebiasis is frequently characterized by pain in the right side of the chest, dyspnea if any considerable area of the lungs is involved, rise in temperature

and leukocyte count, and not uncommonly expectoration of considerable amounts of a pinkish or reddish-brown purée in case the lesion erodes into a large bronchiole or a bronchus.

8 Amebic invasion of other viscera produces inflammatory disease of these organs, usually not definitely demonstrable anatomically except at exploratory operation or at necropsy.

9. Amebiasis cutis is recognized clinically as a relatively circumscribed lesion with elevated, semi-fibrosed margins, a dark-reddish periphery and an undermining necrotic center.

10 All extra-intestinal types of amebiasis are secondary to infection which originally became established in the large intestine.

Chapter 5

Diagnosis, Treatment and Prognosis of Amebiasis

DIAGNOSIS

IN the diagnosis of amebiasis there are two possible diagnostic procedures, clinical and laboratory. A physician who has extensive experience with this disease may, on the basis of the patient's history and physical findings, entertain a strong suspicion of amebic colitis, but clinical evidence is not conclusive Therefore, it is essential that in each clinic and hospital there be properly qualified laboratory workers to provide substantive proof of the infection Nevertheless, "it must be stated clearly that the physician in charge of the patient is professionally responsible for the interpretation of the laboratory findings If a positive dependable laboratory report of *E histolytica* is returned, then it is necessary to determine in the light of the clinical picture if the findings are of primary, secondary or incidental clinical importance. This the physician must decide and on this decision depends the management of his patient If the laboratory diagnosis is negative on the basis of a single stool examination, and a clinical suspicion of amebiasis still exists, other stool specimens should be examined, supplemented by saline-purged or enema specimen . Thus, it is evident that the laboratory is an essential supplement to the clinical examination and evaluation, but

in no sense does it relieve the physician of his responsibility" (Faust, 1950, 1952).

CLINICAL DIAGNOSIS

Intestinal amebiasis. It has been emphasized in Chapter 4 that there is no pathognomonic sign, symptom or syndrome which can be relied upon to provide definitive proof of intestinal infection with *E. histolytica*. Any of the more acute symptoms previously described may create a strong suspicion of amebic etiology, and the patient's history may provide additional circumstantial evidence. X-ray findings with reference to hypermotility of the large intestine, or showing filling defects or cicatricial areas, may support the suspicion; and proctoscopic visualization of lesions may increase the presumption. Yet relatively few cases of this disease conform to the classical picture; many patients have less tangible intestinal signs and symptoms, and a still larger number have asyndromic manifestations Even in the Chicago hotel epidemic a considerable proportion of the acute dysenteric cases were misdiagnosed on clinical grounds (Craig, 1944), while the colitis which developed in the Tokyo apartment house epidemic was not suspected of being amebic in origin for more than a month after it appeared (Ritchie and Davis, 1948). Thus, cumulative evidence points to one conclusion, namely that reliable laboratory confirmation is required to clinch a clinical diagnosis of intestinal amebiasis.

Hepatic amebiasis. The situation with reference to hepatic amebiasis is somewhat different. Although it has been indicated that the picture of incipient hepatitis associated with amebic colitis (Sodeman, 1950a, 1950b) is as yet too obscure to be properly evaluated, the syndromes of amebic hepatitis *sensu stricto* and amebic liver abscess have been studied carefully and constitute relatively reliable criteria for diagnosis. Moreover, in amebic hepatitis it may be difficult or impractical

to obtain direct demonstration of the etiologic agent. Likewise, early recognition and treatment of amebic hepatitis are important, in order to forestall the possible development of abscess. Thus, clinical diagnosis of amebic hepatitis and amebic liver abscess, even though unsupported by laboratory evidence, is frequently justified, provided the clinical pictures are characteristic. Sodeman (1950a), and De Bakey and Ochsner (1951) have provided relatively clear descriptions of these two stages of hepatic amebiasis

In amebic hepatitis the only conspicuous hepatic manifestations are enlargement and tenderness, and there are likely to be low-grade fever and modern leukocytosis, at times also chills, profuse perspiration, anorexia, nausea and vomiting Usually the margin of the liver can be palpated below the right costal margin anteriorly, but difficulty may be experienced in palpation because of the acute tenderness and rigidity of the abdominal muscles in this quadrant

In amebic liver abscess hepatomegaly and tenderness are also encountered, although the latter is not usually as exquisite or extensive as in amebic hepatitis. Since a majority of amebic abscesses occur near the dome anteriorly in the right lobe of the liver, roentgenography usually shows a bulging elevation and immobility of the right leaf of the diaphragm, encroaching on the lower right pulmonary field, with obliteration of the cardiophrenic angle Fever, when present, is of low grade, and the total leukocyte count is somewhat higher than in amebic hepatitis but does not approximate the count in acute pyogenic infections Loss of weight and weakness are more conspicuous than in the earlier stage of hepatic amebiasis. De Bakey and Ochsner (1951) stress the importance of the relatively slight increase in neutrophilic leukocytes in hepatic amebiasis in contrast to the much greater percentage of neutrophiles in pyogenic infection, and emphasize the usefulness of the complement fixation test in amebic involvement of the liver. This latter

point will be considered under specific laboratory procedures (page 89).

Diarrhea or dysentery is not a necessary antecedent or accompaniment of hepatic amebiasis. This "fact deserves particular emphasis, for it is not sufficiently appreciated. Unfortunately, the fallacious impression still exists that diarrhea, whether as an antecedent or accompanying manifestation, occurs with significant frequency in amebic hepatitis and hepatic abscess. Actually, a *relatively high proportion* of patients will not give a history of diarrhea" (De Bakey and Ochsner, 1951).

LABORATORY DIAGNOSIS OF AMEBIASIS

While the x-ray and the hemogram contribute valuable information, the term "laboratory diagnosis" in the sense in which it is employed here is restricted to specific diagnosis of amebiasis, by (1) demonstration of the etiologic agent itself or (2) proof of its presence by immunologic tests. These two methods of diagnosis will now be considered.

DEMONSTRATION OF *ENDAMOEBA HISTOLYTICA*

Before discussing the sources from which *E. histolytica* may be obtained for diagnosis and the approved methods of diagnosis, it is necessary to point out that intelligent, well-trained, experienced diagnosticians are required for this service. Competence is not acquired in the standard courses offered in schools of medical technology, but only after several months of daily training under skilled direction in laboratories with an abundance of fresh diagnostic material (Faust, 1952). Until recent years there were relatively few individuals whose diagnosis of amebiasis could be relied upon. Even today expert laboratory workers sometimes fail to agree among themselves

on the interpretation of microscopic findings in excreta, exudates and aspirates in which *E. histolytica* may occur.

For specific diagnosis of intestinal amebiasis reliance is placed primarily on recovery of *E. histolytica* from the stool, saline purges and enema specimens. At times proctoscopic aspirates, scrapings, biopsies and necropsies add valuable diagnostic information. For diagnosis of extra-intestinal amebiasis, aspirated, biopsied and autopsied material are examined. Occasionally an amebic abscess may spontaneously burst and its contents become available for examination.

The stool. This is the total intestinal evacuation and consists of fecal material, and at times mucus, blood and sloughed tissue débris. If the stool is normally formed or semi-formed, it [illegible]

simple rules are helpful in selecting particular portions of the stool for examination and anticipating the stage of the ameba likely to be found in positive stools.

Unless satisfactory stools are available for examination time and effort may be wasted. Freshly evacuated formed stools may be kept for 24 hours at a temperature of 20 to 22°C, and for a week to 10 days in the icebox without loss of the diagnostic characters of encysted *E. histolytica* which they may contain. Unformed stools should be examined within an hour, preferably a half hour after they have been passed, in order that amebic trophozoites which may be in the stool may not lose their motility. *E. histolytica* is not too well preserved in bulk stools, such material submitted to the laboratory usually constitutes a diagnostic liability. This conclusion is reached with profound regret, since it frequently excludes the diagnostic service of good laboratories at a distance from the source of clinical material.

The stool specimen to be examined should be free of oil, magnesia, bismuth, barium or other extrinsic materials which will obscure microscopic observations of protozoa. It should be passed in a clean container and free of urine. It should be processed as follows.

Direct, double-coverglass fecal film. This should be prepared from each stool to be examined. While ordinary 1 x 3-inch microscopic slides may be employed, a tidier preparation, without risk of contaminating the microscope stage, can be made if 1½ x 3-inch slides are used. Coverglasses, 22 mm square, No. 2 thickness, are most practical. For best results both slides and coverglasses should be scrupulously clean A small drop of physiologic saline is placed somewhat to the left of center on the slide, a small amount of feces (about one to 2 mgm., or the size of a small grain of sand) is transferred with a wooden applicator from the specimen to the saline, in which it is thoroughly mixed, and the film is mounted with a coverglass. To the right of this film a drop of iodine solution* is placed on the slide, a fleck of feces thoroughly mixed in this solution, and the film mounted with a coverglass. The two films, the left side unstained and the right side iodine-stained, should be separated from one another by a space of about 2 mm., so that the iodine will not diffuse into the unstained preparation. The film should be thin enough so that newsprint can be easily read through the mounts

The unstained side is examined for the active stage of *E. histolytica* and other intestinal protozoa; the stained side, par-

*D'Antoni's iodine or, if this is not available, a filtered saturated solution of iodine crystals in one per cent potassium iodide made up volumetrically. *Lugol's solution is too strong and "burns" the more delicate protozoa*

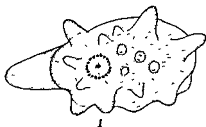
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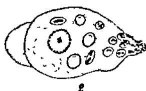
for several months

ticularly for protozoan cysts. On the basis of its specific cytologic characteristics *E. histolytica* can usually be differentiated from the other protozoa present in the film. The appearance of the more common intestinal protozoa in the trophozoite and cystic stages, using the iodine-stained preparation for the latter, are illustrated in Figures 11 and 12.

Concentration technics for recovery of protozoan cysts from feces Frequently protozoa in the stools are too scant in number to be found consistently in the small random sample of stool employed in making the direct fecal film. Trophozoites can not be satisfactorily concentrated from the stool by routine procedures, but cysts of amebas and other intestinal protozoa are readily separated from the feces and concentrated in a diagnosable, living condition by employing the zinc sulfate centrifugal flotation technic developed by the author and his associates for this particular purpose (Faust *et al.*, 1938). After suspending about 0.5 gm (or cc) of feces in 10 cc of tapwater and straining through two layers of dampened surgical gauze into a Wassermann tube, the operator spins the suspension in the centrifuge at 1500 rpm for one minute, decants the supernatant fluid, and resuspends the sediment in water. The suspension is then recentrifugalized and the supernate entirely drained off. Zinc sulfate solution of specific gravity 1.180 is now added to the sediment which is thoroughly suspended in it. After recentrifugalization the tube is allowed to come to complete rest, after which the surface film is transferred with a bacteriologic loop to a drop of iodine on a slide. The preparation is finally mounted with a coverglass and is examined microscopically for protozoan cysts. Not only is the yield of cysts very satisfactory and their diagnostic quality excellent, but the medium is clean and relatively free of fine particulate objects, including bacteria, which at times obscure the cysts in the direct fecal film.

On the average not more than 20 to 27 per cent of positive

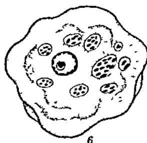
































50 microns

E.C.F.

(see legend on following page)

cases of *E. histolytica* are detected by a single stool examin tion using the 2-coverglass direct fecal film preparations. E adding the zinc sulfate concentration technic the diagnosti

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FIGURE 11 Trophozoites of the intestinal amebas of man.—*Endamoeba histolytica* (1–5) 1, active trophozoite with several finger-like pseudopodial extensions, nucleus having central karyosome and peripheral chromatin beads, ingested red blood cells but no bacterial inclusions in the cytoplasm, 2, ameba with ingested red blood corpuscles and bacterial inclusions in the cytoplasm, dragging many bacteria in its wake, 3–5, typical change in form of an active trophozoite in a few seconds' time

Endamoeba coli (6 and 7) Trophozoites with characteristic viscous cytoplasm, broad sluggish pseudopodia, nucleus having excentric karyosome and coarse peripheral chromatin, and numerous cytoplasmic food vacuoles containing bacteria

Endolimax nana (8–10) Trophozoites showing characteristic limpid pseudopodial extensions, finely granular ("milky") endoplasm, nucleus with massed karyosome, and cytoplasmic food vacuoles containing bacteria

Iodamoeba bütschlii (11–13) Trophozoites with dense cytoplasm and sluggish pseudopodia, nucleus with stellate karyosome, dense glycogen mass in 11 and 13, and cytoplasmic food vacuoles containing bacteria.

Dientamoeba fragilis (14–16) Trophozoites with delicate cytoplasm, nucleus (at times two nuclei) with central mass of chromatin beads and cytoplasmic food vacuoles containing bacteria Only the trophozoite stage of *D. fragilis* is known While this ameba is more commonly observed in diarrheic stools, it may be found in flecks of mucus incorporated in formed or semiformed feces (Original.)

FIGURE 12 Cysts of the common protozoa of man as seen in fresh fecal films stained with D'Antoni's iodine The karyosome and peripheral chromatin, and at times the chromatoidal bars, stand out as practically unstained in contrast to the yellowish-brown of the cytoplasm, the glycogen in most species stains a diffuse mahogany brown, but in *Iodamoeba bütschlii* it is a densely-staining compact mass 1–5 cysts of *Endamoeba histolytica*, with chromatoidals; 5, with diffuse glycogen mass 8, 9, cysts of *Endolimax nana* 12, 13 cysts of *Iodamoeba bütschlii* 6, 7, 10, 11, cysts of *Endamoeba coli*, with diffuse glycogen mass 14, 15, cysts of *Chilomastix mesnili* 16, cyst of *Giardia lamblia* (From chart prepared under the author's direction The reproduction used here has been colored to show the characteristic staining reaction of fresh cysts when treated with D'Antoni's iodine.) (Original adaptation.)

zoites because of its relatively alkaline pH (approximately 9) Sodium sulfate (Glauber salts), with a pH of 8, and buffered phospho-soda, with a pH of 7, appear to evacuate the active amebas in an uninjured condition because the medium is more nearly isotonic, and are therefore recommended for this diagnostic procedure

In examining the saline-purged specimen the formed fecal elements which are usually passed first are discarded and the terminal liquid portion is utilized Cellular material and mucus passed in this portion are allowed to settle to the bottom of the container into which the specimen is passed, some of this sediment is pipetted directly onto a dry slide, mounted with a coverglass and examined microscopically for active trophozoites

If saline purgation is contraindicated, an equally useful specimen for examination may be obtained by employing a high enema of tepid physiologic saline As in the purged specimen, sedimented cellular débris and mucus passed in the liquid portion are most likely to contain evidence of infection Obviously this method is not practical for routine diagnosis but in special cases it is very valuable

Culture technic If diagnosable cysts of *E histolytica* are present in the stool they can be apprehended by the direct fecal film or in the zinc sulfate concentrate (see above) There is therefore no need to culture the cysts Furthermore some cysts fail to excyst and grow in amebic culture media If trophozoites in the unformed stool exhibit typical *E histolytica* motility and locomotion, culture is likewise not needed However, there are instances in which a dysenteric or diarrheic exudate, as well as sediment in the liquid portion of a saline-purged or enema specimen, suggest *E. histolytica* trophozoites, although no diagnosable *E histolytica* trophozoites are found Under these circumstances the cellular detritus and mucus may be planted in an amebic culture medium, incubated at 37°C for

48 hours and the sediment then examined for amebas Occasionally this method provides positive results when all direct attempts at specific diagnosis have failed. (For methods of cultivating *E histolytica in vitro* the reader is referred to Craig and Faust, 1951, pp. 868 and 870)

Material obtained at proctoscopy. Ulcerated patches in the rectum or adjacent segment of the colon which are visualized at proctoscopy may or may not be due to *Endamoeba histolytica*. In acute infections in which the lesions are of recent development their architecture may suggest amebic origin, but it is always helpful if the clinical suspicion can be confirmed by demonstration of active trophozoites of the pathogen. To this end aspirated material or scrapings from under the margin or from the depth of the ulcer, and at times punch biopsies, are obtained The former two types of material are for direct examination after mounting the specimen between a slide and a coverglass. The biopsy specimen may also be directly examined but is more often fixed in formalin, sectioned and stained before search for amebas is made. In all three types of material the stage of *E. histolytica* which is found in the tissues is the trophozoite, not the cyst. Cysts may be present in flecks of feces or mucus adherent to the surface of the lesion but not in the invaded tissues themselves.

Examination of proctoscopic aspirates and scrapings is frequently confusing and difficult because of the contracted, and at times distorted appearance of the host tissue cells present in this material. Persons skilled in the diagnosis of cellular exudates in the stool require special training to interpret the cellular elements in proctoscopic material. The difficulty results particularly from the way in which rounded-up epithelial cells and polymorphonuclears may simulate precysts and cysts of *E. histolytica* or macrophages resemble the trophozoites. As a result of misinterpretation many false diagnoses of amebic colitis

have been made. Antiamebic treatment, prescribed on the basis of this type of diagnosis, has obviously failed to relieve the patient of his symptoms or to eliminate these "precysts" and "cysts."

The only safe diagnosis of *E histolytica* from unfixed proctoscopic material is based on demonstration of a living, motile ameba, with the characteristic progressive movement of active *E histolytica* trophozoites It should never be attempted on rounded-up cells resembling amebic cysts A negative diagnosis is much more consistent than a positive one made on isolated cells or clumps of cells which suggest *E. histolytica*.

If careful, competent study is made of the patient's stools, supplemented by freshly passed saline-purged or enema specimens, proctoscopic material will not usually provide any considerable number of additional cases of infection with *E histolytica* (Hood, Sodeman and Akenhead, 1952). In the author's experience and that of his colleagues in the Tropical Medicine Clinic of Tulane University, amebiasis is frequently diagnosed by stool examination when proctoscopic material is negative This is understandable, since a majority of the sites of amebic invasion of the large bowel are above the levels which can be examined proctoscopically If the patient to be proctoscoped has been adequately prepared by saline purgation, most of the trophozoites and cysts of *E histolytica* and other protozoa free in the large intestine will have been washed out of the bowel previous to proctoscopy, and diagnosis will have been made on the sediment from the purged specimen

Punch biopsy specimens obtained proctoscopically, which are fixed, sectioned and stained for study, at times provide definite proof of amebic proctitis

Material obtained from extra-intestinal foci. This consists of aspirates or biopsied specimens, and may be obtained from practically any organ or tissue suspected of harboring *E. his-*

tolytica. As in intestinal amebiasis, so in extra-intestinal complications, the organism occurs in tissues only in its trophozoite stage.

The most common location outside the intestine from which aspirates are obtained for the diagnosis of *E. histolytica* is the liver. Because of the multiple microscopic locations of the amebic lesions during the stage of acute amebic hepatitis, aspiration is not routinely carried out, and the likelihood of aspirating amebas from the midst of one or more of these minute lesions is indeed very small On the other hand, the liver abscess is usually large enough so that it can be located roentgenographically with considerable accuracy. Moreover, in certain cases there is need to aspirate the necrotic purée from the abscess center before healing will occur. Ordinarily *E. histolytica* can not be recovered from the semi-liquid sauce which is withdrawn from the center of the abscess cavity, although the author has seen the active organisms in freshly aspirated purée. More commonly the amebas will be recovered from aspirates obtained from just within the rim of the abscess cavity, among hepatic cord cells which are being invaded.

Aspirates, scrapings and biopsied specimens from other extra-intestinal viscera, as well as from the skin, should be prepared for study and examined as recommended for intestinal and hepatic lesions of amebic origin. (See above.)

Necropsy material. Most necropsy material on amebiasis is unsatisfactory for diagnosis because the amebas have died and lost their diagnostic integrity before autopsy was performed. In general, if more than four hours have elapsed *post mortem*, *E. histolytica* trophozoites in the tissues will have become nonmotile, rounded up, their cytoplasm will have become coarsely granular and their nuclear chromatin will have lost its specific diagnostic characters. However, if sections of formalin-fixed material are stained with hematoxylin-eosin, then counterstained with Best's carmine, the glycogen in the amebas will be

stained a strawberry-pink, so that the amebas will stand out distinctly against the host cells. This can be easily observed under low power of the microscope and provides a dependable diagnosis after the detailed structural characteristics of the organism have been lost.

Previous to four hours after death amebic trophozoites in the tissue usually retain their diagnostic integrity. They can be removed from the tissues and examined directly as a coverglass smear, or placed in culture media, with a reasonable expectation that they will live and multiply, although routine procedure is to fix a suspected segment of tissue, then section and stain it for microscopic examination.

IMMUNOLOGIC DIAGNOSIS OF AMEBIASIS

The only type of immunologic test which has been successfully carried out in amebiasis is complement fixation. Izar (1914) is usually credited with the first reported evidence that in amebiasis the blood of man and experimentally infected animals contains complement-fixing antibodies. However, it was not until 1927–1928 that Craig removed this test from the interesting but relatively obscure academic field to one of clinical importance when he announced his own serological experiments on amebiasis and soon thereafter (1929) published a precise technic for conducting the test. During the past quarter century many serologists have employed this test or a modification of the test, partly as an experimental procedure and partly on a practical basis, to compare results with coprological and clinical findings. Although there have been considerable discrepancies in the results obtained by various investigators, the following conclusions seem to be justified: (1) *Endamoeba histolytica* produces complement-fixing antibodies which can be demonstrated in the blood serum of natural and experimental infections, (2) the test is specific and under ideal con-

ditions should not give false positives; (3) the test is apparently more strongly positive when the amebas are intimately associated with the host's tissues; (4) the test becomes negative soon after the amebas are eradicated from the body; and (5) in order to place the test on a practical basis there is critical need for a reliable, potent antigen which is commercially available.

Craig (1929–1937) used absolute alcohol to extract his antigen from very large numbers of *E. histolytica* trophozoites in the bloody mucus discharges of experimentally infected dogs. Employing a human hemolytic system, in 175 *E. histolytica* patients over an eight-year period he obtained 90 per cent agreement with coprologically-positive findings. His antigen was sensitive enough to pick up asymptomatic infections as well as clinical cases of amebic colitis and amebic liver abscess. Rees *et al.* (1942) prepared a more consistent, purer source of antigen by growing *E. histolytica in vitro* in the presence of a single, non-pathogenic bacterium (organism *t*). These workers extracted the antigen in physiologic saline. Bozicevich (1950, 1951) has furnished evidence that a reliable antigen should be polyvalent, i.e., it should consist of a pool of antigens from several strains of *E. histolytica*, since antibody is more sensitive to homologous than to heterologous antigen.

The more recent reports (Kent and Rein, 1946; Hussey and Brown, 1950; McDearman and Dunham, 1952) on the use of antigen prepared according to the technic of Rees *et al.* (*l c.*) and obtained from the same source, are in agreement, that the Rees type of antigen is of greater diagnostic value for hepatic amebiasis than for amebic colitis

The complement fixation test for amebiasis has not yet been placed on a sufficiently dependable foundation for general diagnostic use. Most of the essential facts with reference to the technic are known, yet antigen is not available for use in the clinical laboratory. This is a goal which must be attained, since

there is a real need for the test, not to replace stool examination for *E. histolytica* but to check stool diagnosis, particularly after antiamebic treatment has been administered; it is likewise particularly useful in cases of extra-intestinal amebiasis in which it is frequently impractical to obtain aspirated or biopsied material from the lesion.

DIFFERENTIAL DIAGNOSIS

Intestinal Amebiasis. Although the laboratory provides specific evidence of amebic colitis, there are a number of diseases which must be considered in making a differential diagnosis, and on which the history, symptoms and physical examination contribute substantial background information. A few of the diseases which must be excluded are shigellosis, brucellosis involving the colon, tuberculosis and carcinoma of the rectum, and hemorrhoids. Roentgenography and proctoscopy, as well as the hemogram, culture procedures and immunologic tests for bacteria, all these constitute important aids. Moreover, amebiasis may be superimposed on any of these diseases of the colon or rectum, so that specific diagnosis of one does not exclude the others.

Extra-intestinal Amebiasis. Since probably not more than 5 per cent of patients with amebic colitis have hepatic amebiasis, a preponderant number of disease conditions of the liver associated with amebic colitis will be due to other causes, including infectious hepatitis and related hepatic disease of virus etiology, Weil's disease, relapsing fever, tuberculosis, syphilis, hydatid cyst, carcinoma, acute yellow atrophy, fatty degeneration of the liver, and hepatic cirrhosis of various etiologies. It has been pointed out (page 76) that the clinical manifestations of acute amebic hepatitis and amebic liver abscess are relatively pathognomonic, hence the physician experienced with these conditions will usually have little difficulty in making

a differential diagnosis. Moreover, amebiasis of the pleura and lungs is commonly a sequel to amebic liver abscess so that this complication should not pose a serious diagnostic problem. However, amebiasis of the brain and other organs infrequently invaded is not likely to be suspected etiologically and is seldom diagnosed specifically except on exploratory operation or at autopsy. Similarly, amebiasis cutis may not be considered from an etiologic standpoint unless scrapings or biopsy reveal amebic trophozoites in the lesion (Engman and Meleney, 1931).

TREATMENT

Treatment of amebiasis has the double objective of relieving the patient of his symptoms and eradicating the causative agent, *Endamoeba histolytica*. In practice, therapeutic agents are available which serve three purposes, viz., (1) relief of symptoms; (2) specific attack on the ameba; and (3) attack on bacteria which have invaded the amebic lesions. In addition, surgical intervention is at times indicated, particularly in extra-intestinal foci of the disease. It may be necessary to combine two or more of these therapeutic measures to obtain the objective.

INTESTINAL AMEBIASIS

1. Relief of symptoms. This refers primarily to severe tenesmus, cramps, exhausting diarrhea or dysentery and marked dehydration which may be experienced in acute amebic colitis. Sodeman (1952) advises three types of palliative measures, viz., (a) to reëstablish better fluid balance, one should administer fluids orally or parenterally and at times give transfusions; (b) to control cramps, employ atropine, 0.6 mgm., or powdered opium, 30 mgm., three times daily until relief is obtained; and (c) to relieve the dysentery or diarrhea, prescribe emetine hy-

drochloride, 6 per cent solution, administered subcutaneously, in the amount of one milligram per kilo of body weight daily, but not in excess of a daily total of 65 mgm., for a maximum of four to six days.

NOTE *Emetine* has a low rating for killing *Endamoeba histolytica* in the intestinal wall (15–20 per cent), and *is employed in amebic colitis only for symptomatic relief*, and not in excess of the indicated amount. This warning should be carefully heeded since emetine is a potentially dangerous myocardial toxicant. During its administration the patient should be kept in bed under close observation and electrocardiograms should be made during and subsequent to administration of the drug. If signs of myocardial damage appear administration must be terminated immediately.

2. Specific anti-amebic therapy. For direct action on the amebas in amebic colitis the earlier chemotherapeutic agents which were widely employed, e.g., ipecacuanha and emetine hydrochloride, have been superseded by drugs which have higher amebicidal potency and at the same time are better tolerated. It must be kept in mind, however, that as more precise diagnostic technics have been developed for detecting *E. histolytica* in the stools, many persons previously considered "cured" following a standard course of anti-amebic therapy are now found to harbor a residual infection. This stricter post-treatment criterion of "cure" has resulted in a more accurate appraisal of the real amebicidal value of standard drugs employed in the treatment of amebic colitis, as well as new ones being tested. Moreover, while test-tube experiments and therapeutic tests on experimentally infected animals may provide important leads on the comparative efficacy of such drugs, the only real test in human amebiasis consists in clinical trials of drugs in which there are sufficiently treated and controlled cases, so that significant conclusions can be drawn. In other words, clinical investigation rather than laboratory experiment or opinion con-

stitutes the ultimate criterion as to the amebicidal value of the drug.

For amebic colitis there are currently available three groups of drugs, each of which contains two or more members that have high anti-amebic properties and are relatively well tolerated. None of these drugs can be guaranteed to eliminate *E. histolytica* from the human intestinal tract, yet approximately 90 per cent or more of persons with amebic colitis can be freed of their infection by use of one or a combination of two or more of these therapeutic agents. While from a public health point of view it is useful to know if an anti-amebic drug kills the amebic cysts in the lumen of the colon of carrier cases, clinically the *essential question is, what is the effect of the drug on the amebic trophozoites living in the intestinal wall*

The most valuable amebicides in intestinal amebiasis belong to the following groups: (1) iodo-hydroxyquinolines; (2) arsonic acid derivatives; and (3) certain antibiotics.

IODO-HYDROXYQUINOLINES

Three members of this group have a high potential in the treatment of amebic colitis, viz., (a) chiniofon, (b) diiodoquin and (c) vioform. In addition, another iodo compound, emetine bismuth iodide, will be considered. All are administered orally.

Chiniofon U.S.P (Yatren, Anayodin; 8-hydroxy-7-iodoquinoline-5-sulfonic acid) has been employed for the treatment of amebic colitis since 1921, and is one of the most satisfactory anti-amebic agents. The adult course of treatment consists of the administration of 4 x 0.25 Gm. tablets taken orally *three* times daily (3 Gm. daily) before meals for seven or eight days. Although chiniofon is absorbed rather sparingly from the intestinal wall into the blood stream, it rapidly kills amebic trophozoites with which it comes in contact. It rarely produces

iodine idiosyncracy but in some patients it causes a rather profuse, although not painful diarrhea. This results from hypermotility of the colon and has a helpful effect in clearing the trophozoites out of subsurface cul-de-sacs, whereupon the amebas are rapidly killed in contact with the drug. [illegible] severely dehydrated patients, administration of chiniofon should be discontinued and diiodoquin substituted. High retention enemas of chiniofon (2 per cent solution of the powder in warm water) have frequently been employed to supplement oral administration of the drug. The cure rate for chiniofon is probably about 80 to 85 per cent.

Diiodoquin U.S.P. (Diodoquin; diiodo-oxyquinol [illegible] diiodo-8-hydro [illegible] treatin [illegible] is mor [illegible] amebic [illegible]. The adult course of treatment consists of the administration of 3 or 4 x 0.65 Gm tablets taken orally three times daily (maximum daily, 2 50 Gm.) before meals for 20 days. Unless the patient has an iodine idiosyncracy no side effects need be anticipated. The reported cure rate is 80 to 90 per cent.

Iodochlorohydroxyquine U S P (Vioform, 5-choloro-7-iodo-8-quinolinol) was first reported to have valuable anti-amebic properties in 1931 and is extensively used for this purpose in Latin America under the name Enterovioform. It is the most readily absorbed of the halogenated hydroxyquinolines employed in the treatment of intestinal amebiasis. The adult course of treatment consists of the administration of 1 x 0 25 Gm capsule taken orally four times daily (1 0 Gm daily) for 10 days (Anderson, 1952). Like chiniofon, vioform may produce profuse diarrhea, hence should not be prescribed for severely dehydrated patients. Vioform has never gained popu-

lar acceptance in the United States but probably deserves more sympathetic consideration.

Emetine bismuth iodide B.P. (bismuth emetine iodide) is a British product which has been extensively employed in tropical and Oriental countries to treat amebiasis. The recommended adult course of treatment consists of the administration of 1 x 0.2 Gm. salol-coated capsule or tablet daily for seven to 10 days, taken orally at night two hours after a light meal, and "preceded if necessary by some sedative mixture, phenobarbitone, 2 grains, or tincture of opium, 15 minims," to stop vomiting (Napier, 1946). It may likewise be advisable that the patient remain in bed during the course of treatment. Emetine bismuth iodide has no valuable anti-amebic properties which can not be supplied by other amebicides which are much better tolerated

ARSONIC (ARSANILIC) ACID DERIVATIVES

Three members of this group are available for treating intestinal amebiasis, viz., acetarsone, carbarsone and Milibis, while clinical trials of the thioarsenilates have shown that they have potential usefulness.

Acetarsone N.F. (Stovarsol; N-acetyl-4-hydroxy-m-arsanilic acid) was the earliest arsenical employed as an amebicidal agent (Marchoux, 1923). The adult course of treatment consists of the administration of 1 x 0 25 Gm. tablet taken orally three times daily (0.75 Gm. daily) for one week, followed by one tablet daily for two weeks. Although the cure rate is relatively high, the toxic reactions are usually pronounced, consisting of acute intestinal distress, hepatitis, and at times severe exfoliative dermatitis. Except in France and French territories acetarsone has been replaced by better tolerated anti-amebic drugs.

Carbarsone U.S.P. (p-Ureidobenzenearsonic acid) has been

employed as an anti-amebic agent since 1932 (Read, Anderson, David and Leake, 1932), and has been administered to many thousands of persons harboring *E histolytica*. It has both cysticidal and trophozoiticidal potency and is particularly useful in eliminating this ameba in carriers (Craig, 1944) The usual adult course of treatment consists of the administration of 1 x 0 25 Gm tablet taken orally twice daily (0 5 Gm daily) for 10 days. Treatment may be repeated after an interval of 10 days Although carbarsone has relatively low toxicity, arsenic-sensitive individuals have at times experienced diarrhea, nausea, intestinal colic and dermatitis Should any of these symptoms develop, the administration of carbarsone should be terminated and a non-arsenical anti-amebic drug substituted

Milibis (bismuth glycolylarsanilate NNR) has recently received clinical acceptance as a valuable anti-amebic drug (Berberian, 1948, Berberian, *et al*, 1950) Tests on several thousand cases of amebic colitis by a number of physicians (Hoekenga, 1952, Berberian, Dennis and Korns, 1952, Sodeman and Beaver, 1952) have confirmed the earlier findings The recommended adult course of treatment consists of the administration of 1 x 0.50 Gm tablets taken orally three times daily (1 5 Gm daily) before meals for eight days In a series of 461 cases of intestinal amebiasis given one to four courses of treatment, each case having one to eight follow-up stool examinations, 381 (82.6 per cent) were reported to have become free of *E histolytica* (Anonymous, 1951) Milibis is relatively insoluble, is rather slowly absorbed by the intestinal wall and is therefore primarily useful in early acute amebic infections or in asymptomatic cases It is stated to have low toxicity Nevertheless caution should be exercised in prescribing this drug for persons who have arsenic idiosyncracy Browne, McHardy and Edwards (1950) and Sodeman (1951) have reported symptoms of encephalitis, neuritis and exfoliative dermatitis during or following administration of Milibis

Thiocarbarsone (4-carbamido-phenyl bis [carboxymethylthio] arsenite) has been under clinical trial and is commercially available. It has been tested by Anderson *et al.* (1947) and Sodeman and Beaver (1952), and found to be very effective as an anti-amebic agent. With reference to its toxicity, Anderson and Hansen (1950) state that the thioarsenites "have been found to exert topical effects on the gastric mucosa similar to but less harmful than those produced by arsine oxides." The treatment consists of the administration of 2 x 50 mgm. Enseals-coated tablets three times daily for 10 days. Patients should be observed for arsenic sensitivity.

ANTIBIOTICS

Certain antibiotics, such as penicillin and streptomycin, have no direct amebicidal or amebostatic effect in doses sufficient to kill or inhibit growth of enteric bacteria. Other antibiotics which are equally effective against a wide bacterial spectrum have detectable but relatively ineffective action against *E. histolytica* in therapeutic doses. A third group which are likewise potent against bacteria and fumagillin have remarkable amebicidal properties.

Direct amebicidal action. The antibiotics with anti-amebic action which have been tested clinically include aureomycin, terramycin and bacitracin. According to Tobie, Most *et al.*, (1951) both aureomycin and terramycin have a 100 per cent anti-amebic efficiency lasting for two weeks following a tolerated course of treatment; but at 2½ months the ameba-free persons in the aureomycin series had dropped to 60 per cent, whereas terramycin retained its perfect record up to at least six months. These studies were conducted on asymptomatic carriers and therefore do not necessarily reflect the efficacy of these or other antibiotics in cases of acute amebic colitis (Most, Miller and

Grossman, 1950; Frye *et al.*, 1952) The recommended adult dosage of *terramycin* (terramycin hydrochloride NNR) is 1 x 0 25 Gm. capsule taken orally four times daily (1 o Gm. daily) for 10 days; that of *aureomycin* (aureomycin hydrochloride USP), 2 x 0.25 Gm capsules taken orally four times daily (2 o Gm. daily) for 10 days In therapeutic doses the patient may experience mild anorexia and nausea, in excessive doses there may be more disagreeable side effects

Bacitracin NNR has been given clinical trial by Most, Miller and Grossman (1950) In a series of 51 patients having amebiasis varying in severity from fulminating dysentery to asymptomatic infection, 48 became ameba-free during treatment, but 14 of these had positive stools six to 350 days after the last dose of the antibiotic had been administered In eight of the severe cases clinical and parasite cure was obtained, and in one of these bacitracin was curative after other amebicidal drugs, including aureomycin, were ineffective Of the 43 mildly symptomatic or asymptomatic cases 80 per cent cure was apparently secured. The calculated probable percentage of cures for a single course of treatment, consisting of 80,000 units taken by mouth daily (about 2 o Gm daily) for 10 days is 66 Toxic effects from oral administration are stated to be negligible

Recently fumagillin has shown remarkable specific anti-amebic activity (Anderson, 1952)

3. Attack on associated bacteria As early as 1914, Hargreaves (1945) discovered that sulfa drugs and penicillin were valuable adjuvants in the treatment of chronic cases of amebic colitis which had proven refractory to specific anti-amebic medication. These drugs do not directly affect the amebas but help in cleaning up secondary infection in the amebic ulcers preparatory to specific anti-amebic therapy. Streptomycin, chloramphenicol and other antibiotics which also have no direct action on the amebas, as well as aureomycin, bacitracin and ter-

ramycin, are similarly useful. This fact has not received the attention which it deserves at the hands of physicians treating cases of amebic colitis.

In early uncomplicated cases of intestinal amebiasis it is usually not necessary to employ antibiotics, since the iodohydroxyquinolines and arsonic acid derivatives will be curative. Moreover, Knight and Tarun (1952) have called attention to the fact that antibiotics may temporarily upset the equilibrium of the intestinal flora and in this way prolong intestinal symptoms even after the amebas have been eradicated. However, in chronic intestinal amebiasis, or in acute amebic colitis in which there is symptomatic evidence of bacterial complications, it is advisable to administer chemotherapeutic agents which have both anti-bacterial and anti-amebic action. This effect may sometimes be obtained by employing aureomycin, bacitracin or terramycin alone, at other times by combining a non-antibiotic amebicide with an effective bactericidal agent.

EXTRA-INTESTINAL AMEBIASIS

Until very recent years emetine hydrochloride was the sole available therapeutic agent with demonstrated specific action on amebic infection outside the intestinal tract; none of the drugs which are more effective than emetine hydrochloride in treating amebic colitis are particularly useful in extra-colonic amebiasis In 1948 Conan (1948a) published a preliminary report on the value of chloroquine in hepatic amebiasis Sodeman *et al* (1951) state that "the effectiveness of chloroquine in hepatic amebiasis has been clearly confirmed," although "this drug, like emetine, is not always effective," and "failure to respond to chloroquine does *not* rule out amebic hepatic disease." Nevertheless, Murgatroyd and Kent (1948), Emmett (1949), Sodeman *et al.* (1951) and other workers have been successful in eradicating active *E. histolytica* with chloroquine

bicidal in other extra-intestinal foci to justify its use; (2) its administration by mouth is simple; and (3) its toxicity is low, so that hospitalization is not required if the patient is ambulatory. The recommended dosage for *chloroquine* in extra-intestinal amebiasis is a loading amount of 0.6 Gm. of the base (1.0 Gm. chloroquine phosphate USP) by mouth daily for two days, followed by 0.3 Gm. (0.5 Gm. chloroquine phosphate) daily for two to three weeks (Conan, 1949). For *emetine hydrochloride* USP, the maximum daily schedule is one mgm. per kilo of body weight (but never in excess of 65 mgm.), administered subcutaneously, for a period not exceeding 10 to 12 days, following which an interval of 20–30 days must elapse before a second course may be administered, to guard against cumulative toxic effects of the drug (Sodeman, 1952). "By attention to cardiac rate, which may increase, and to blood pressure, which may fall, damage to the cardiac muscle can be avoided. With excessive dosage the electrocardiogram shows depressed T waves and other abnormalities" (Anderson, 1952).

In all cases of extra-intestinal amebiasis not only should therapy be instituted to eradicate the amebic infection in the extra-intestinal focus, but simultaneously, or as an immediate follow-up, adequate amebicidal treatment should be instituted to guarantee that E. histolytica *has been eradicated from the primary lesions in the intestinal wall.* Specific therapy for amebic colitis provides the only assurance that an active or silent focus of the disease in the colon will not produce additional extra-intestinal lesions

For *chemotherapeutic control* in amebiasis, please refer to Chapter 6, page 93.

PROGNOSIS

Fifty years ago acute amebic dysentery, frequently with amebic liver abscess, almost invariably had a grave prognosis. Even

today an undiagnosed case of acute or chronic amebic colitis may have an equally fatal termination. Yet with increased consciousness on the part of the physician that *Endamoeba histolytica* may be responsible for a great variety of symptoms, together with modern methods of diagnosis and treatment, the prognosis with respect to recovery is excellent to good, provided the infection is recognized early, its etiology is confirmed, and appropriate therapeutic measures are carried out before there has been extensive, irreversible tissue damage.

The relatively high incidence of amebiasis throughout the world and its hyperendemicity in many areas make it impractical, in fact impossible to diagnose and treat all cases of the infection. Possibly the individual physician feels helpless in the face of the knowledge that on the average 10 per cent of his patients harbor *Endamoeba histolytica* Or possibly he is impressed by the argument that an overwhelming majority of infected individuals do not suffer from the infection and that this parasite may conceivably live as a commensal in the human colon without endangering the health of its host (Hoare, 1950, Miller, 1952) The facts remain that amebiasis is an important clinical problem; that many so-called symptomless carriers suffer from vague symptoms which disappear when accurate diagnosis of amebiasis is made and adequate therapy is instituted, and that symptomless infections today may transform into symptomatic colitis or amebic hepatitis tomorrow

Amebiasis is not only a serious clinical problem, it is likewise a very important public health problem For the individual patient the prognosis of amebiasis rests largely with the practicing physician; for the community it lies primarily within the province of community hygiene. Its public health aspects are considered in Chapter 6

Summary

1. Accurate diagnosis of intestinal amebiasis can not be made on clinical grounds alone, since the symptoms are not sufficiently pathognomonic to provide definitive evidence of the infection. Thus clinical suspicion of amebic colitis requires confirmation by laboratory procedures.
2. The clinical characteristics of amebic hepatitis and amebic liver abscess are usually sufficiently distinctive to justify the institution of therapeutic procedures even when confirmatory laboratory evidence is lacking.
3. Laboratory diagnosis of amebiasis is based on (a) demonstration of the etiologic agent, *Endamoeba histolytica,* and (b) immunologic reactions.
4. Formed stools of positive cases will contain *E. histolytica* in the encysted stage; unformed stools, saline-purged and enema specimens, as well as tissue aspirates and biopsied material, will contain the trophozoite stage. Methods of obtaining *E. histolytica* and of differentiating it from other intestinal protozoa consist of the following types of microscopic preparations: (a) the direct fecal film, unstained and iodine-stained (or hematoxylin-stained); (b) zinc sulfate concentrates of cysts present in small numbers in the feces; (c) mucus and cellular débris sedimented from purged and enema specimens; and (d) microscopic preparations of tissue aspirates or biopsied and necropsied specimens. Training and experience are a prerequisite to dependable microscopic diagnosis of *E. histolytica.*
5. Immunologic evidence is provided by the complement fixation technic. Present-day complement fixation methods are much more reliable in the diagnosis of hepatic amebiasis than of amebiasis of the intestine.

6. Treatment of amebiasis is aimed at (a) relief of symptoms and (b) eradication of the etiologic agent.
7. In intestinal amebiasis symptomatic relief is accomplished by reëstablishing better fluid balance, use of atropine or opium to counteract pain, and administration of emetine hydrochloride to relieve profuse dysentery or diarrhea
8. Present-day anti-amebic drugs valuable in the treatment of amebic colitis belong to three groups: (a) iodo-hydroxyquinolines; (b) arsonic acid derivatives; and (c) certain antibiotics. In the first group are chiniofon, diiodoquin, vioform and emetine bismuth iodide; in the second group, acetarsone, carbarsone, Milibis and thiocarbarsone, and in the third group, terramycin, aureomycin, bacitracin and fumagillin Antibiotic therapy is frequently advised in chronic amebic colitis to clean out bacterial invasion of amebic ulcers preparatory to specific anti-amebic treatment
9. In extra-intestinal amebiasis chloroquine is the drug of choice, particularly in hepatic amebiasis, emetine hydrochloride, although acknowledged to be efficacious, is second choice because of its greater toxicity.
10. In the treatment of all cases of extra-intestinal amebiasis specific treatment for intestinal amebiasis is likewise indicated to remove the primary focus of the infection.
11. Although amebiasis of 50 years ago almost invariably provided a poor prognosis, with more modern concepts of its protean manifestations, more accurate diagnostic technics and more effective and better tolerated amebicidal drugs, present-day prognosis is excellent to good, provided recognition, diagnosis and treatment are undertaken early in the disease.

Chapter 6

Control of Amebiasis

INTRODUCTION

IN order to understand the scope of the control problem of amebiasis it is necessary to realize that this is a widely disseminated, endemic-hyperendemic disease, with epidemic outbreaks. For the most part it is insidious in its development and deceptive in the damage which it produces in the human body. Only occasionally, when a considerable number of persons acquire acute amebic colitis during an epidemic, do physicians, public health workers and the public at large become awakened to its more dramatic potentialities. Then it may have the psychologic appeal of poliomyelitis, influenza, smallpox, typhus fever or bubonic plague.

The greatest number of published articles on amebiasis in the United States appeared during the three-year period 1934–1936 following the Chicago hotel epidemic of 1933, on patients who acquired acute amebic dysentery in that hotel, as well as on other infected population groups in the United States (D'Antoni, 1949a). In some respects this temporary interest paralleled that on amebiasis among British veterans of World War I following their return home from service overseas (Dobell, *et al.*, 1918). In the United States the stimulus which was produced in 1933 was not sustained. The Public Health Service was unwilling, and at the time, because of lack of sufficiently

trained personnel, was unable to accept the challenge of control of this disease A few years later the Preventive Medicine Service, Office of the Surgeon General, U. S Army was apathetic to appeals made to it by American students of the disease at the beginning of World War II, when military personnel were being sent into tropical war areas. Only when large contingents of the fighting forces became temporarily incapacitated as a result of amebic colitis, did the Epidemiological Board of the Army become conscious of the debilitating effects of amebiasis. And for several years thereafter many veterans who had chronic sequelae of the disease crowded Veterans Hospitals and consulted private physicians in an attempt to regain their health.

If success is to be achieved in the control of amebiasis, this disease must be accepted as a public health problem Wherever amebiasis occurs it must be detected, accurately diagnosed and consistently reported to local, state and federal health authorities. Wright (1950) has provided evidence of the inadequacies and inconsistencies which exist in the reporting of amebiasis by the several States. In some States reports are based solely on clinical evidence, and in other States amebic dysentery is not differentiated from dysentery of other etiology, in 16 States laboratory confirmation is required before reporting, and in 13 States reports originate from laboratories without clinical evaluation of the infection While there has been a slight increase in reported cases between 1933 and 1947 (viz, from 2,057 to 3,130), with a total of 41,781 for the 15-year period, this cumulative number constitutes less than 0 03 per cent of the estimated total proportion of persons in the United States (10 per cent) who have the infection (Craig, 1944) It is clear from these figures that only an insignificant number of cases of amebiasis are reported In some States amebiasis is still not a reportable disease, but undoubtedly most of the failure in reporting is lack of recognition and diagnosis of amebiasis.

Life insurance companies have taken an overly cautious position with reference to amebiasis. If an applicant for insurance has ever been diagnosed as having amebiasis, it is extremely difficult for him to obtain an insurance contract even though the infection may have been eradicated several years earlier. On the other hand, persons who have never been examined for amebiasis are granted insurance provided they meet the minimum requirements of the medical examiner, which do not include fecal examination for amebiasis (D'Antoni, 1949b). This discrimination is as unwarranted as that which prevailed a few years ago with respect to applicants who were denied insurance because they had a history of malaria or lived in an area where malaria had existed (Faust, 1939). Such practices *are not only unjust but are likely to discourage disease reporting*

A program for the control of amebiasis in the United States or elsewhere in the world must be well-conceived, it must include all important methods of control, it must be set up on a practical basis, and must be well organized and planned over a long period of years. This requires the willing cooperation of practicing physicians, health officers and the public. Since this is a public health problem, the initiative must be taken by health officials.

As a major premise to this campaign it must be accepted that effective control of amebiasis is a highly desired goal, because (1) the disease is clinically important; (2) is no respecter of age or race; and (3) is widely disseminated in a considerable proportion of the populations of temperate as well as warm climates. What, then, are the practical methods of attack, and what may be expected from such a campaign to control amebiasis?

The basic methods of control of any infectious disease are derived from its epidemiologic pattern, e.g., its means of propagation and particularly the modes of human exposure to the

etiologic agent. While much valuable new data will unquestionably be obtained in an intensive prolonged program for the control of amebiasis, the fundamental epidemiologic information on amebiasis is a matter of record. (See Chapter 2 of this monograph.)

Amebiasis is contracted from infected hosts through contaminated water, food, food handlers, filth flies and cockroaches, fomites, directly from person to person, at times possibly from moist soil, and under certain circumstances from reservoir hosts. Methods of control will be considered under each of these major topics.

WATER

Water is a potential and likely source for exposure to viable cysts of *Endamoeba histolytica* which have been evacuated in human excreta and have gotten into the water supplies in sewerage effluents or from promiscuous defecation of infected individuals, and it has been demonstrated that dilution of the contaminated feces with large volumes of water greatly prolongs the life of the cysts (Boeck, 1921).

Water supplies for municipalities are obtained wherever possible from uncontaminated sources, yet many large cities depend on rivers containing variable amounts of particulate matter in suspension, including pollution from sewage. Most of this water is sand-filtered and/or sedimented with alum floc which usually allows fairly rapid settling and a clear supernate. If there is still potential danger from enteric bacteria, as detected by the *Escherichia coli* index, an additional safeguard is provided by chlorination (one ppm.). Although standard filtration and flocculation will produce a settling out of many of the viable *E. histolytica* cysts in such water and standard chlorination procedure will kill many of those remaining, some may retain their vitality and in grossly contaminated water will con-

stitute a source for human infection. The amount of nascent chlorine necessary for effective destruction of the cysts is 3 ppm residual after 30 minutes (Newton, 1950), an amount which is distinctly unpleasant to smell and taste.

Smaller supplies of drinking water may be rendered practically non-infective with respect to amebic cysts by use of filters of diatomaceous earth (Lowe, *et al.*, 1944), by hyperchlorination (Fair, 1948), by halogenization with iodine (Matheson and Stoll, 1944), and, of course, by boiling.

An important point in sanitary engineering in homes, hotels, office buildings and factories is to insure that back-flow of sewage is properly trapped, so that it does not contaminate the incoming fresh-water supply. Faulty cross connections were found to be responsible for the Chicago hotel epidemic of 1933, when sewage heavily laden with viable *E. histolytica* cysts contaminated the water supply in the individual guest rooms (Bundesen, 1944; McCoy *et al.*, 1936b).

In suburban and rural homes dependent on septic tanks or outdoor privies and on water supplies from shallow wells, care must be taken that the water is not fouled by seepage from contaminated soil. To guarantee safe household water, it may be necessary to relocate the site of the cesspool or privy, and to provide a concrete platform and curb for the well to prevent surface contamination, or to dig a deeper water supply to be pumped up through seepage-proof pipe.

FOOD AND FOOD-HANDLERS

Food may be contaminated from liquid human nightsoil used to fertilize garden crops, from grossly polluted water in which green vegetables and fresh fruits are washed, from food-handlers who are careless about their personal hygiene, or from flies which convey cysts of *E. histolytica* from fresh deposits of human excreta to food in the kitchen or on the dining table.

CONTROL OF AMEBIASIS

Nightsoil contamination. This is a potential hazard in countries where human excreta are used to fertilize garden crops, such as lettuce, radishes, water-cress, celery, and strawberry beds. In many countries of Europe, as well as in the Orient, the need for human fertilizer is so great and commercial fertilizer so difficult to obtain that great hardship would result if the population were deprived of the use of human manure to enrich the soil. The danger of contracting amebiasis exists only when fresh excreta are used; it may be averted if the fertilizer is properly ripened or is sterilized with ammonium sulfate (as little as 0.7 per cent), which in itself is a valuable fertilizer.

Contamination from grossly polluted water. This applies to salad greens and fruits to be eaten raw. Water of questionable purity used for washing otherwise clean leafy greens and fruits to be eaten raw should be filtered, boiled or treated with chlorine or iodine (see above, page 110), so as to insure that it is free of viable amebic cysts.

Individual precautions which may be taken in areas where there is suspicion of fecal contamination of garden crops include the following: (1) Abstain from eating green salads such as lettuce, water-cress, celery and unpeeled radishes, (2) thoroughly immerse salad greens in undiluted vinegar (5 per cent acetic acid) for 10 to 15 minutes before serving (Beaver and Deschamps, 1949b), and (3) immerse fresh strawberries for a few seconds in a boiling syrup, then drain and chill in the ice-box.

Food handlers. The handling of food, including green salads, fresh fruits, cold meats, etc., by unclean cooks and service attendants constitutes a very serious breach in community hygiene. In Chapter 2 of this monograph it has been pointed out that there is a significant correlation between *E. histolytica* carriers who are food handlers and the incidence of infection with *E. histolytica* in the immediate community. Clinical amebiasis is likewise excessive among individuals served by these

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food handlers, whether they be mothers or servants in the home (Meleney, 1930; Andrews, 1933) or food handlers in public eating places (Kaplan *et al.*, 1927; Tomney *et al.*, 1933; Winfield and Chin, 1939; Schoenleber, 1911). The author has considerable unpublished data supporting this conclusion.

The problem of examining food handlers in a large community to detect infection with *E. histolytica* is a formidable task (McCoy and Chesley, 1931). In the first place, a corps of competent laboratory workers is required. This is less of an obstacle in the United States today than it was in 1933, since most state and city board of health laboratory directors and technicians have obtained satisfactory training in the diagnosis of amebiasis (Faust, 1952). In the second place, proprietors of restaurants resist examination of their employees for fear their establishment will be regarded unfavorably. Yet with proper education of the public an official certificate of inspection, stating that all cooks and waiters are free of amebiasis (following competent diagnosis and adequate treatment), *should add greatly to the prestige of the establishment rather* than black-list it. This is an aspect of amebiasis control which is capable of solution but will require extensive education of the public, possibly legislative action at the state level to compel its execution, and a considerable amount of time for its accomplishment.

A third difficulty encountered in examining food handlers in public eating places is the rapid turn-over of these persons, amounting to as much as 100 per cent per year. Since efficacious well-tolerated drugs are now available for treating amebiasis, the possibility might be considered of periodic mass therapy of all food handlers in public establishments, employing a chemotherapeutic agent such as diiodoquin which would not cause absence from work during treatment. If this plan were adopted there would be no need for laboratory diagnosis on each food handler, only checkups before inauguration of

the program and from time to time after it had been in operation, to determine its value

The more difficult control problem with respect to the food handler and amebiasis concerns this source of transmission in the home, particularly in the case of mothers and servants in close contact with small children (D'Antoni, 1949a) It will not be feasible to discover the great majority of these *E histolytica* carriers, hence it will be necessary to teach them the danger of passing on the infection from unclean fingers and to instill in them the need for careful washing of their hands immediately after visiting the toilet This must not consist merely of rinsing the hands but thorough scrubbing with soap and water. Such instruction is a task primarily for the visiting public health nurse, who can eventually accomplish much by repeated tactful suggestion and demonstration This education in methods of hygiene should be integrated with the general health program of the community

Filth-flies. Just as in the mechanical transmission of salmonellosis, typhoid fever and shigellosis, filth-flies constitute a serious potential menace in endemic and epidemic amebiasis Wherever in a home or community, particularly in a rural area, *E histolytica* cyst passers deposit their excreta in open privies or other sites accessible to feces-eating flies, there is the likelihood that viable cysts consumed by these flies may be deposited hours later in their vomit drops or minute fecal dejecta on food in the kitchen or on the dining table

In 1945 and 1946 there was justifiable hope that fly control could be satisfactorily accomplished by use of DDT and other insect toxicants, employing area spraying and especially residual spraying on the walls inside of homes But rapidly developing resistance to these insecticides has largely banished this hope (Decker and Bruce, 1952, Harrison, 1952) While area spraying with DDT at times of heavy filth-fly breeding may temporarily reduce the fly population, reliance must be

placed primarily on the elimination of the breeding places. In so far as amebiasis is concerned, this means that outdoor latrines must be kept fly-tight. Likewise, effective screening of doors and windows constitutes an important preventative to keep the flies out of the home, hence away from human food This method of control for amebiasis can be conducted by sanitarians in connection with campaigns to prevent the other insect-borne diseases.

Cockroaches. These household pests are very difficult to control in warm climates Although chlordane, piperonyl butoxide, phosphorus toxicants, and to a considerably lesser extent DDT, are effective in killing cockroaches in closed quarters, the flying roach (*Periplaneta americana*), which is prevalent in the southern United States, enters from the outside when door-screens are opened or when there are other means of gaining access to kitchens and bathrooms. In order to control the German roach (*Blatella germanica*), which is primarily a house breeder, meticulous care must be taken to keep all foods tightly covered and kitchen and bathroom drains free of saponified fats and grease.

Fomites. Clothing and play objects, which have been soiled by children who are *E. histolytica* cyst passers, at times constitute important sources for contracting amebiasis (Ivanhoe, 1943). Personal cleanliness, especially after visiting the toilet, constitutes the objective for control of this breach in home sanitation.

Person-to-person contamination. In discussing the epidemiology of amebiasis (Chapter 2), reference has been made to the excess of this infection in prisons, mental hospitals and children's asylums over that of the surrounding population. In the former two types of institutions gross evidence of excreta within the wards provides adequate explanation for the high frequency of the infection, particularly when the inmates are crowded together and their bodily filth is readily transferred

from one person to another (Berberian, Dennis and Korns, 1952). Even in the absence of gross fecal contamination in children's homes person-to-person contact constitutes a major exposure hazard. This same type of exposure to amebiasis prevails in the general population of certain rural areas in temperate climates and is even more pronounced in tropical climates, where large families live in very congested quarters, and seldom bathe or wash their clothes.

Among the institutionalized groups it may be possible to provide periodic intensive programs to clean up the surroundings, although in wards of mental hospitals housing the incurably insane instruction in the simple rules of personal hygiene will be wasted (Berberian, Dennis and Korns, *l.c.*). The more humane handling of these individuals in private wards or cubicles rather than like cattle in open wards would help to produce better sanitation. In the population at large where there is a high incidence of amebiasis the level of personal and group hygiene will need to be raised. This is perhaps the most difficult task confronting the program of amebiasis control. Nevertheless, since so large a segment of the ameba-infected population in certain countries lives under the stigma of a disease-producing environment of overcrowding and neglected sanitation, a general program of environmental improvement, together with training in the elementary rules of health, should aid appreciably in the control of amebiasis.

Moist soil as an exposure source for amebiasis. In tropical areas where there is daily rainfall and children defecate promiscuously on the soil, viable cysts of *E. histolytica* may be recovered from the polluted soil (Beaver and Deschamps, 1949a). This constitutes a relatively constant potential source for exposure for children who frequent these infested sites. Instruction of mothers and children in the elements of personal hygiene and environmental sanitation is indicated.

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suppressive dosage, and, most important of all, the need to provide mass therapy for all individuals in the institution, since reinfection rapidly takes place in close contact with untreated persons who are infected.

Sodeman and Beaver (1952) have also published findings on mass treatment of 341 feeble-minded persons of all ages in a Mississippi institution in which amebiasis was hyperendemic. One hundred and seventeen, all in one housing area, with an infection incidence of 10.2 per cent before treatment, received chiniofon (4 x 0.25 Gm. tablets three times daily for eight days); all in another housing area, with pre-treatment incidence of 15.8 per cent, were given diiodoquin (3 x 0.21 Gm. tablets three times daily for 20 days); 138, all in a third housing area, with pre-treatment incidence of 34.1 per cent, were given Milibis (2 x 0.25 Gm. tablets three times daily for eight days), and 29, all in a fourth housing area, with pre-treatment incidence of 34.5 per cent, thioarsenites (2 x 50 mgm. tablets three times daily for 10 days). Stool examinations for the respective groups two to five weeks after completion of the treatments were as follows: chiniofon, 1.7 per cent positive for *E. histolytica*, or 83.3 per cent reduction; diiodoquin, Milibis and thioarsenites, no positives, or 100 per cent success. Toxic manifestations were relatively uncommon, but minor side effects were experienced in each group, the most unpleasant of which occurred in those to whom thioarsenites were administered. Examination one year later of two stools each of 149 individuals who had taken diiodiquin or Milibis revealed no evidence of *E. histolytica*. All new admissions or readmissions following mass treatment have been submitted to full amebicidal therapy to prevent the entrance of new infections from the outside.

These three chemotherapeutic studies on the control of amebiasis demonstrate that mass therapy in institutionalized or otherwise relatively restricted communities is both effective and

practical, provided all individuals are treated simultaneously and all new admissions or readmissions are given treatment, to prevent reexposure to infection This constitutes a valuable weapon in the control program for such groups

EDUCATION AND THE CONTROL OF AMEBIASIS

Not only must the physician and the public health worker become better acquainted with the epidemiologic background of amebiasis, and the physician more familiar with the clinical problems which result from this infection, but physician, sanitarian and layman must all cooperate in its control First of all amebiasis must be accepted as a major public health problem Its story can be told in simple language which a child with grammar school training can understand This information can be incorporated by visual aid technics in lessons in hygiene in the city and rural schools, in parent-teachers meetings, in contacts between the public health nurse and mothers in the home, and in local groups interested in public health improvement in their communities It is probably no exaggeration to state that amebiasis in the United States today is as serious a public health liability as tuberculosis, not because it takes more lives but because its insidious course is so inadequately known and appreciated by public health leaders and its debilitating effects are so difficult to detect and evaluate

In urging that the importance of amebiasis be recognized and that knowledge concerning methods of exposure, clinical consequences of the disease and practical measures of control be incorporated into public health programs, the author at the same time cautions against "amebophobia" or scare propaganda concerning amebiasis. Such an attitude on the part of physicians and health officials, particularly if publicized in popular newspaper accounts, can do irreparable harm. The public health attack on amebiasis must be a sane one, based on

been demonstrated to be effective in heavily infected communities not subject to institutionalized regulations

The control of amebiasis must have a recognized place in the broad program of health education in the community The story of how the disease is contracted, what its clinical consequences may be, and how individual hygiene and environmental sanitation will contribute to its control, should be incorporated in lessons in hygiene in the public schools, in discussions at parent-teachers meetings, and in the public health nurse's contacts with mothers in the home

Scare propaganda concerning amebiasis, particularly in the public press, are to be deplored Factual information can and must be presented Only by sane, united, constructive effort can the disease be brought under control

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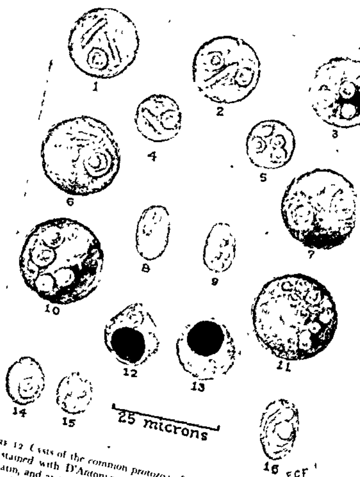


FIGURE 12 Cysts of the common protozoa of man as seen in fresh fecal films stained with D'Antoni's iodine. The karyosome and peripheral chromatin, and at times the chromatoidal bars, stand out as practically unstained in contrast to the yellowish brown of the cytoplasm; the glycogen in most species stains a diffuse mahogany brown, but in *Iodamoeba butschlii* it is a densely staining compact mass. 1–5, cysts of *Endamoeba histolytica*, with chromatoidals; 3, with diffuse glycogen mass. 8, 9, cysts of *Endolimax nana*. 6, 7, 10, 11, cysts of *Endamoeba coli*. 12, 13, cysts of *Iodamoeba butschlii* with diffuse glycogen mass. 14, 15, cysts of *Chilomastix mesnili*. 16, cyst of *Giardia lamblia*. (From chart prepared under the author's direction. The reproduction used here has been colored to show the characteristic staining reaction of fresh cysts when treated with D'Antoni's iodine.) Original adaptation.

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This Book

Amebiasis

By ERNEST CARROLL FAUST, A B, M A, PH D

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